PERIODONTAL DISEASE, BONE LOSS, AND ANTI-ANDROGEN THERAPY

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Submitted to the Graduate Faculty of

the Department of Epidemiology

of the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

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It was defended on
6 September 2005

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University of Pittsburgh, 2005

Periodontitis is a multifactorial disease with microbial dental plaque as the etiological agent. The manifestation and progress of periodontitis is influenced by a wide variety of determinants and factors, including subject characteristics, social and behavioral factors, systemic factors, genetic factors, the microbial composition of dental plaque, and others. The pathogenesis of periodontal disease results in resorption of alveolar bone and loss of the attachment apparatus to the teeth. There is a biological potential that periodontal destruction may be influenced by systemic bone loss. Since alveolar bone loss is a prominent feature of periodontal disease, disturbances in bone mineral density (BMD), especially in the jaws, are suspected of being an aggravating factor in periodontal disease. In previously published research, the severity of osteoporosis may be related to tooth loss in post-menopausal women. Considering the relationship among bone mineral density, osteoporosis, and periodontitis in men, it is known that men completing androgen ablation therapy for control of prostate cancer are at higher risk for osteoporosis. As androgen deprivation therapy is the recommended treatment for men with metastatic or locally-advanced nonmetastatic prostate carcinoma, and as prostate carcinoma is the most common visceral malignancy and the second leading cause of death from cancer in men, the relationship between androgen deprivation therapy and loss of bone mineral density is a matter of public health importance.

This dissertation assesses the association between bone mineral density, the presence of periodontal disease, and the possible subsequent onset of clinical osteoporosis, as seen among a population of older women followed longitudinally; a set of men with prostate carcinoma undergoing androgen ablation therapy; and those men in the same set not receiving androgen ablation for prostate cancer. We believe our research, using the model of periodontal bone density and oral bone loss, shows additional clear empirical evidence pointing to a cause-and-effect relationship between androgen deprivation therapy and loss of bone mineral density.

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Periodontal disease is a local chronic inflammatory disease of the tooth-supporting tissues, characterized by inflammation of those tissues. The disease has a prevalence of thirty-five (35) percent in the adult population of the United States (Consensus Report *Annals of Periodontology* 1996; Consensus Report *Journal of the American Dental Association* 1998), and is a major cause of tooth loss and edentulism among adults. Periodontal destruction---pathologic inflammation of the gingival and hard tissues---often results in bone loss in the jaw, mobility of teeth, and ultimately tooth loss. The health and social impacts of periodontal disease are enormous and adversely influence nutrition, speech, oral function, and facial esthetics.

The pathogenesis of periodontal disease results in resorption of alveolar bone and loss of the attachment apparatus to the tooth. There is the biological potential that periodontal destruction may be influenced by systemic bone loss (Consensus Report *Annals of Periodontology* 1996). Since alveolar bone loss is a prominent feature of periodontal disease, disturbances in bone mineral density (BMD), especially in the jaws, are suspected of being an aggravating factor in the case of periodontal disease (Wactawski-Wende *et al.* 1996).

Our incomplete understanding of the role of various risk factors obscures the specific causes and underlying mechanisms of the periodontal disease process (Albandar 2002, Albandar 2002). Established risk factors for periodontal disease include dental plaque, calculus, smoking, systemic disease, stress, and genetic traits. It is clearly documented that the incidence of periodontal disease increases with advancing age. Significant age-demographic shifts exist in the United States populations and, as people live longer and retain more teeth, the number of people developing periodontal disease is expected to increase in the next few decades. Changes in our knowledge of the etiology of periodontal disease, and better recognition of the potential importance of the susceptibility factors as they affect the initiation and progression of periodontal disease, have led to an intense study of specific risk factors for periodontal disease.

Several convincing epidemiologic studies, such as the surveys conducted by the National Center for Health Statistics (Ronderos 2004) and those of the National Institute of Dental and Craniofacial

Research (NIDCR), with additional studies from abroad, have challenged the popular perception that humans have a universal susceptibility to periodontal disease (Irfan 2001).

The relationship of osteoporosis in men and periodontal disease due to androgen ablution is not well established. Studies to evaluate the relationship between osteoporosis due to androgen ablution and periodontal disease are essential for enhancing our understanding of systemic bone pathogenesis. The objective of this research is to assess, and thus better understand, the association between bone mineral density, the presence of periodontal disease, and the possible subsequent onset of clinical osteoporosis, as seen among a set of men with prostate carcinoma undergoing androgen ablation therapy, and those in the same set not receiving androgen ablation for control of prostate cancer.

1.1 THE ETIOLOGY AND EPIDEMIOLOGY OF PERIODONTAL DISEASE

Periodontal disease is a pathological condition, a chronic inflammatory disease, affecting the supporting structures of teeth, characterized by inflammation of the teeth-supporting tissues at the gums. Periodontal disease is identified by a bacterial challenge that can destroy the host tissues, the response leading to periodontal attachment loss, bone loss, and ultimately possible tooth loss (Nunn 2003; Consensus Report *Annals of Periodontology* 1996; *Journal of the American Dental Association* 1998).

Thus, *periodontitis* is clearly a multi-factorial disease with microbial dental plaque as the initiator (Nunn 2003; Consensus Report *Annals of Periodontology* 1996; *Journal of the American Dental Association* 1998). However, the manifestation and progression of periodontitis is influenced by a wide variety of determinants and risk factors, including subject characteristics, social and behavioral factors, systemic factors, genetic factors, the microbial composition of dental plaque, and others (Nunn 2003; *Annals of Periodontology* 1996; *Journal of the American Dental Association* 1998). If periodontitis is not treated, the disease will slowly progress and painlessly destroy the bone which supports the teeth. Untreated, the disease will eventually cause tooth loss.

1.1.1 The epidemiology of periodontal disease: Prevalence and incidence

Although many epidemiological studies have been conducted concerning periodontal disease using the parameters of clinical attachment level, attachment loss, probing pocket depth, and gingival recession, the evidence pertaining to prevalence, incidence, and risk factors in an older adult population of either sex is limited (Albandar 2002).

The NHANES III (1994) study showed that among dentate adults in the United States (six teeth or more present) age 30 and older, 3.1 percent had *advanced periodontitis* (defined as pocket depth upon probing greater than 6mm); 9.5 percent had *moderate periodontitis* (defined as pocket depth upon probing 4-6 mm), 21.8 percent had *mild periodontitis* (defined as pocket depth upon probing 3-5 mm) and 65.5 percent had *no periodontitis* (defined as pocket depth less than 3 mm). The prevalence of periodontitis (all severities) increases steadily with increasing age (Albandar 2002, Albandar 2002). Using the measure of tooth loss to definitively diagnose *periodontitis* in his six-year study, the youngest age group (18-33) presented at baseline with the fewest mean number of teeth lost (1) and concluded with the least (0). Subjects over age 57 entered with the most teeth lost (3.6), and concluded with the most teeth lost (0.4).

Periodontal disease and aging are commonly thought to be correlated with each other. The relationship is intuitively thought to be more related to the breakdown of the periodontal tissues over time, rather than an actual function of the accumulation of chronological years causing a deficiency that increases the individual's susceptibility to periodontal disease (Nunn 2003; Genco 1996). Epidemiological studies have shown more periodontal disease, both in terms of attachment loss as well as bone loss, among older age groups than younger age groups (Grossi *et al*. 1994; Grossi *et al.* 1995; Streckfus *et al.* 1999). Other research has shown that certain physiological changes in the periodontium occur with age (Johnson *et al.* 1989 and van der Velden 1984) *although these physiological changes alone are not responsible for the breakdown in the gingival tissues* (the gingival recession, the attachment loss, the eventual tooth loss).

Pocket probing depth is the measure from the free gingival margin (FGM) to the base of the sulcus/pocket with the use of a calibrated probe (*HuFriedy Michigan 0 probe, diameter of probe is 0.5 mm*). Pocket depth is probed on six sites per tooth (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual). Clinical periodontal attachment level and the loss of periodontal attachment are defined as the distance in millimeters (mm) from the cementoenamel junction (CEJ) to the base of the pocket. Probing depth is the distance from the free gingival margin (FGM) to the base of the sulcus/pocket. Other essential periodontal measures are the presence or absence of gingival recession or gingival bleeding, and the measures of supragingival plaque and calculus. Gingival bleeding will be measured as (0: no bleeding; 1: bleeding); supragingival plaque will be measured as (0: no plaque; 1: plaque). Calculus will be measured as (0: no calculus; 1: supragingival calculus).

Among adult Americans, males have a greater prevalence of periodontitis than females. Albandar (2000) reports that different racial and ethnic groups within a given population show marked differences in periodontal disease indicators, and the general diagnosis of periodontitis. An important finding of the NHANES I study was the trend that African-Americans in the U.S. population have a much higher occurrence of periodontitis than Caucasians (1.28 to 0.76 respectively, using the general indicator of

Periodontal Index) and a higher prevalence of periodontitis than Mexican-Americans. Non-Hispanic whites had significantly less periodontitis than either of the other two racial groups (Albandar 2002). The same ratios were confirmed in Albandar's 2002 study of periodontitis among 14,000 U.S. adolescents (13-17 years old): early onset forms of periodontitis occurred in 10 percent of the adolescent African-Americans, five percent of Hispanics, and 1.3 percent of whites. This gives a prevalence ratio of 7.7 for African-American adolescents, and 3.9 percent for Hispanic adolescents, compared to the white adolescents.

Nunn (2003) points out that race as a risk factor for periodontitis is a complex issue. She notes that *Prevotella intermedia* presents a risk factor for blacks, but not for whites. When socioeconomic risk factors for periodontitis were not considered, blacks were three times more likely than whites to exhibit advanced periodontal destruction. When subjects were in the same socioeconomic status, differences in gum disease often disappeared.

Albandar (2002) takes the conclusions of the NHANES III data regarding gender, race and ethnicity, and the common variables indicating periodontal disease, and presents this data regarding prevalence rate ratios (*duplicated here as Table 1, next page*). In the U.S., adult blacks show the highest prevalence of periodontitis and the most loss of periodontal tissue, followed by Mexican-Americans. Whites show the least disease and tissue loss. As shown in the table, blacks have a much higher probability of having attachment loss and increased probing depth, and Mexican-Americans have a moderately increased probability, compared to whites. For attachment loss ≥3mm, the ratio was 1.26 for blacks, and 1.10 for Mexican-Americans, whereas for attachment loss of ≥5mm, the ratio was 1.73 and 1.28, respectively. Hence, in the U.S. adult population, the probabilities of having attachment loss of ≥3mm and ≥5mm, respectively, were 26 percent and 73 percent higher for blacks and 10% and 28% higher for Mexican-Americans compared to whites. A similar pattern was observed for the other periodontal disease indicators, and is also summarized in Table 1.

1.1.2 The epidemiology of periodontal disease: Periodontal attachment loss

Attachment loss is highly prevalent in the U.S adult population, with more than half (53.1 percent) of subjects 30 years and older showing one or more teeth with 3mm and greater attachment loss, and 32.7 percent of subjects showing 4mm and greater attachment loss (Nunn 2003). The prevalence and extent of attachment loss increased steadily with increasing age, and both parameters were significantly higher in males than in females, and higher in black and Mexican-American individuals than among white subjects *(again, see Albandar's data in Table 1*). In one research report, taking into account different age groups, the distribution of the periodontal disease indicators across the dentist's jaw sextants showed that attachment loss affected most frequently the mandibular incisors and the maxillary molars (Spalj 2003).

Table 1.1 Prevalence rate ratios of periodontal variables, by gender and race-ethnicity
[Data show males v.females (blacks v.whites, and Mexican-Americans v.whites) 30 years and older examined in the third National Health and Nutrition Examination Survey (NHANES III) U.S. 1988-1994]

Variable	Gender	Race-Ethnicity	
	Males/females	Blacks/whites	Mexican-Americans/whites
Prevalence (percent of persons)			
Attachment loss ≥3mm	1.23	1.26	1.10
Attachment loss ≥4mm	1.44	1.46	1.22
Attachment loss ≥5mm	1.55	1.73	1.28
Probing depth ≥3mm	1.14	1.24	1.22
Probing depth ≥4mm	1.46	1.97	1.61
Probing depth ≥5mm	1.73	2.71	1.79
Gingival bleeding	1.17	1.15	1.31
Gingival recession ≥1mm	1.12	1.03	0.94
Gingival recession ≥3mm	1.54	1.29	1.09
Dental calculus	1.02	1.05	1.06
Extent (percent of teeth per person)			
Attachment loss ≥3mm	1.48	1.54	1.17
Attachment loss ≥4mm	1.65	1.75	1.24
Attachment loss ≥5mm	1.93	2.06	1.33
Probing depth ≥3mm	1.39	1.79	1.48
Probing depth ≥4mm	1.63	2.47	1.65
Probing depth ≥5mm	2.00	3.31	1.85
Gingival bleeding	1.24	1.31	1.53
Gingival recession ≥1mm	1.30	1.13	0.95
Gingival recession ≥3mm	1.67	1.49	1.13
Dental calculus	1.21	1.49	1.35

[Data compiled by Albandar *et al.* in 2000]

1.1.3 The epidemiology of periodontal disease: Probing pocket depth

Sixty-four percent of U.S. adults in this study had one or more teeth with a probing depth of 3 mm or greater (*mild periodontitis*). Approximately 22.3 percent had a probing depth of 4mm or greater (*moderate periodontitis*). The prevalence of probing depth at 4mm and greater increased steadily with age. The prevalence and extent of probing depth at 4mm and more was significantly greater among males than in females and among blacks and Mexican–American than whites. Blacks had the highest probing depth measurement among the three race-ethnicity groups (Consensus Report *Annals of Periodontology* 1996; *Journal of the American Dental Association* 1998).

Again, Albandar's data best summarizes all of these periodontal disease indicators---attachment loss, probing depth, gingival bleeding, gingival recession, and dental calculus---related to gender and race and ethnicity (Table 1.1).

1.1.4 The epidemiology of periodontal disease: Gingival recession

In the same study, 22.5 percent of the subjects had gingival recession at 3mm and greater. The prevalence and extent of gingival recession also increased steadily with increasing age: 10 percent of subjects 30-39 years old and 60 percent of subjects 80-90 years old had one or more teeth with 3mm gingival recession. Males had a significantly greater prevalence and extent of gingival recession than females. The prevalence and extent of gingival recession were comparable in the three race ethnic groups (Consensus Report *Annals of Periodontology* 1996).

1.1.5 The etiology of periodontal disease: Summary and risk factors

Clinicians have long believed they had a profile of the patient with periodontal disease, but reviewing the literature regarding the etiology of periodontitis shows little hard evidence to identify the assumed specific predisposing factors (Rees 2003). The profile, according to Rees, includes a patient who is a smoker, is emotionally stressed, possibly malnourished, prone to disease, has a family history of periodontitis, possesses local factors predisposing to the accumulation of plaque (clinically recognizable in short, again, as a smoker with poor oral hygiene) and basically not motivated and not compliant with the oral hygiene maintenance protocols (brushing, flossing, recalls every three, six---at most---twelve, months) and not good at oral hygiene when brushing or flossing is undertaken.

While the profile *is* clinically valid, the risk factors are more profound than the profile indicates, and detailed, thorough, examination of the *underlying* risk factors---the *systemic* risk factors---is warranted and necessary. All persons are not equally susceptible to periodontal disease and do not respond equally well to periodontal therapy. In a classic longitudinal study of a population with no access to dental care and poor oral hygiene (Albandar 1990), enormous variability among individuals in the rates of periodontal disease progression was observed. In this mostly homogenous population, some persons developed disease at very rapid rates, while others had little or no disease progression (Albandar 1990). Again, the established risk factors for periodontal disease are dental plaque, calculus (a hard mineral deposit produced by the action of bacteria and body calcium, requiring removal with instruments by a professional), smoking, systemic disease, age, genetic traits, stress, and others. While each of these factors alone may have a detrimental effect on etiology, prognosis, and treatment outcomes, it should be kept in mind that the presence of any of these factors alone or in combination may influence yet a different outcome (*Journal of the American Dental Association 1998*).

While it is true that some strong current epidemiologic research has challenged the notion that humans face a universal susceptibility to periodontal disease, it is also true that between five and twenty percent of the population have severe forms of periodontal disease. The etiology of chronic adult periodontitis is bacterial in nature, involving pathogens such as *Actinobacillus actinomycetmcomitans, Porphyromonas gingivalis, and Bacteroides forsythus.* Current concepts in the etiology of periodontal disease emphasize systemic factors which may place patients at risk to develop periodontitis. Conversely, periodontitis may be a risk factor in the development of a variety of systemic conditions. A clearer understanding of the relationship between oral health and systemic disease will aid healthcare providers in the management of a variety of conditions and earlier detection and preventive strategies may be developed to address potential systemic problems. A brief closer look at the most current information regarding the association between periodontal disease and the chief systemic risk factors of smoking, diabetes mellitus, obesity, atherosclerosis, hormone replacement therapy, and osteoporosis is worthwhile at this point. We will conclude the risk factor discussion of osteoporosis by transiting into an in-depth look at osteoporosis in men, and then beginning the discussion of our research interest, the relationships between periodontal disease, bone loss and anti-androgen therapy.

1.1.6 The risk factors for periodontal disease: Smoking

Periodontal disease long has been associated with smoking. Although smokers do have greater levels of plaque and calculus than nonsmokers, these factors alone cannot account for the increased incidence of periodontal disease. S.G. Grossi and colleagues found a direct linear relationship between the level of smoking (pack years) and destructive periodontitis even after adjusting for confounding variables such as age, oral hygiene, gender, and socioeconomic status (Grossi *et al.* 1995). Smoking was shown to be a strong risk indicator for periodontal disease, with an odds ratio of 2.0 to 5.0 when evaluating connective tissue attachment loss and 1.5 to 7.0 when measuring bone loss. Zambon and Grossi (1996) further directly concluded that cigarette smoking increased the risk for periodontitis, by increasing the risk for subgingival infection with periodontal pathogens. In other research, Grossi evaluated the effects of smoking and not smoking on healing after mechanical forms of periodontal therapy, such as scaling and root planing (1997) and has also investigated the independent responses of smokers and diabetics to periodontal therapy (1996). Smoking is a major risk factor for destructive periodontal disease and should be addressed when evaluating each patient, regardless of the individual's gender, age, or other risk factors. This deleterious relationship between smoking and periodontal disease is seen in smokers regardless of their overall levels of plaque accumulation. However, the specific microbial flora in smokers may shift to a more pathogenic profile (Van Winkelhoff 2001). There are conflicting reports regarding the effects of smoke on the qualitative and quantitative composition of periodontal pathogens. Recent reports

have shown that the rate of recovery of such harmful pathogens from relatively shallow pockets is greater in smokers (Egger 2001). These finding suggest that tobacco smoking itself may promote the development of local environments that favor the growth of such pathogenic species. Tobacco products may also exert a destructive effect on the periodontium by impairing the normal defense of the host response, or by stimulating the destructive effects of the host response (Person 2001).

1.1.7 The risk factors for periodontal disease: Drinking alcohol

In her comprehensive discussion of the etiology of periodontitis (2003), on discussing the risk factors, Nunn (citing Tezal 2001) summarizes the risk factor of alcohol consumption, concluding that excessive alcohol consumption has been associated with an increased risk of clinical attachment loss as well as an increased risk of gingival bleeding. However, no association between alcohol consumption and alveolar bone loss has been found (Nunn 2003, Tezal 2001).

1.1.8 The risk factors for periodontal disease: Diabetes

The severity of diabetes mellitus (Type I) or non insulin-dependent diabetes mellitus (Type II) is related to the incidence and severity of periodontal disease (Cianciola 1982; Shlossman 1990). Synthesis of collagen appears to be affected by glucose levels. Gingival fibroblasts from diabetic patients synthesize less collagen compared to non-diabetic subjects (Willenshausen-Zonnchen 1991). In addition to finding decreased collagen production in association with diabetes, investigators have found increased crevicular fluid in diabetic patients. The increased crevicular fluid collagenase activity appears to be primarily of neutrophil origin. Interestingly, the increased crevicular fluid collagenase levels found in patients with diabetes can be inhibited *in vitro* by tetracycline (Sorsa 1991). Collagen in a hyperglycemic environment undergoes non-enzymatic glycosylation and cross-linking between the collagen molecules. This collagen cross-linking significantly contributes to reduced solubility and decreases turnover rates. Consistent with this, diabetic gingival collagen shows decreased solubility. Significantly, a return to near-normal solubility of collagen can be achieved by insulin treatment (Sorsa 1991). Also defects in PMN function; induction of insulin resistance (or increased insulin resistance in the diabetic subject); and vascular changes can all contribute to increased susceptibility to infection. Importantly, control of serum glucose levels appears to partly reverse these factors and should therefore be closely monitored with infections.

1.1.8.1 Insulin–Dependent Diabetes Mellitus (Type I)

In initial studies to investigate a relation between periodontal disease and insulin-dependent diabetes mellitus (Type I), the periodontal status of 263 patients was compared to 59 non-diabetics (Cianciola

1982). No periodontal disease was found among subjects under the age of 12, while 13.6 percent of individuals 13- to 18-years-old had periodontal disease. Individuals from 19- to 32-years-old had a prevalence of 39 percent. Investigators noted the duration of diabetes was greater in groups with severe periodontal disease. Thus, it appears that individuals with insulin-dependent diabetes mellitus (Type I diabetes) have an increased risk for developing periodontal disease with age, and the severity of periodontal disease increases with the increased duration of the diabetes.

1.1.8.2 Non-Insulin-Dependent Diabetes Mellitus (Type II diabetes)

Research conducted among Native American communities of (North American) Pima Indians, a population with an extremely high prevalence of non-insulin-dependent diabetes (Type II diabetes), has correlated the relationship of periodontal disease and diabetes. The initial study of periodontal disease in this community [(Nelson 1990) a cross- sectional analysis diagnosing periodontal disease by periodontal attachment loss (tooth loss) and percentage of interproximal crestal alveolar bone loss determined by panoramic radiograph], determined that the rate of periodontal disease in subjects with diabetes was 2.6 times that seen in subjects without diabetes. Regardless of age or gender, subjects with diabetes had a higher prevalence of periodontal disease, indicating that diabetes is a risk factor for periodontal disease.

Further studies among the population showed individuals with non-insulin-dependent diabetes mellitus (Type II diabetes) to be 2.8 times more likely to have periodontal disease defined by clinical attachment loss, and 3.4 times more likely to have periodontal disease defined by radiographic bone loss. The increased risk of developing periodontal disease could not be explained on the basis of age, sex, or hygiene (Emrich Scholossman Genco 1991). A review of the literature on the relationship between periodontitis and diabetes by Soskolne a decade later (1998) reiterated the likelihood of the relationship, and considered the influence of periodontal disease on the control of the diabetic state, confirming the clinical observation that effective control of periodontal infection in patients with diabetes reduces the level of advanced glycosylation end products in the serum. Soskolne concluded that periodontal infection control must be considered an integral part of diabetic control.

Diabetes mellitus Type II and periodontitis are both common diseases in the United States. Many studies have established the clinical observation that periodontal disease may be more severe in patients with diabetes. In fact, periodontal disease has been referred to as the sixth most significant complication of diabetes Type II. Uncontrolled diabetics may present with multiple or frequent periodontal abscesses, generalized gingival swelling and bleeding, and advanced bone loss. It is possible that the increased severity of periodontitis in this population may be related to increased susceptibility, impaired host response, and excessive collagenolytic activity. Periodontal healing may be compromised in poorly controlled diabetics; however, patients who are well-controlled seem to respond as well as non-

diabetics. Diabetic control may be negatively influenced by the presence of chronic infections, such as periodontitis, and treatment of a diabetic patient's periodontal condition may result in more favorable diabetic status. *It is important to recognize periodontal disease as an indicator of a potential underlying systemic condition, such as diabetes mellitus, and consider periodontal health as an important component in the treatment of diabetic patients* (Cianciola 1982; Shlossman and Genco 1990; Pucher 2004).

1.1.9 The risk factors for periodontal disease: Obesity

The growing prevalence of increased body weight and obesity in the United States has raised significant public health concerns (Mokdad *et al.*, writing in the *Journal of th*e *American Medical Association* 1999; also the *American Journal of Public Health* (2004) editorializing obesity as '*the public health challenge of our time*'). Obesity is implicated as a risk factor for several chronic health conditions, is associated with increased mortality, and, moreover, exists in complexes of multiple, clustered, behavioral risk factors. Identified by one group of authors (Fine *et al*. 2004) as among the four most common risk factors contributing to chronic disease [cigarette smoking, risky drinking of alcoholic beverages, physical inactivity, and overweight] and applied to the 2001 National Health Interview Survey, showed that seventeen percent of 29,000 subjects had three or more risk factors for chronic disease. The number of obese people is increasing rapidly in both western and eastern countries [James and others (2001) the report of the International Obesity Task Force (London), analyzing cross-cultural standards of acceptable body mass index, reported in *Obesity Research*]. The health implications of obesity when viewed in conjunction with raised cholesterol and hypertension is cited as the major cause of mortality and disease in Europe (same authors 2004). Obesity is further seen as an issue for developing countries (Caballero 2001) and a review of the literature indicates analyses of the nature of obesity in South Africa, Pakistan, Brazil, China, Mexico, Australia, Gibraltar, Cyprus, Spain, and Greece; among Singaporean Chinese children, French and Italian children, black Jamaican children, postmenopausal Japanese women; and among twenty years of British children.

A 1998 report in *The New England Journal of Medicine* finds a relation between obesity and periodontitis in a healthy Japanese population (Saito Shimazaki Sakamoto). Investigating that relationship is further explored by al-Zahrani and colleagues of Case Western Reserve University (2003), who examined the link between body weight and periodontal disease using data from the third National Health and Nutrition Examination Survey (NHANES III).

A ten-year-old Swedish study concludes that counseling on a balanced diet and smoking cessation by dental professionals might possibly generally improve risk factors for cardiovascular disease (Johansson *et al.*1994). *Adipocytes* in the adipose tissues of obese people produce quantities of biologically active molecules such as leptin, an important molecule regulating energy expenditure and

body weight. Adipocyte-derived active molecules---*adipocytokines*---are candidate molecules accounting for the close association between obesity and other multiple risk factor syndromes.

The proinflammatory cytokine *tumor necrosis factor-alpha* (TNF-alpha) is produced by adipocytes, and its blood concentration is elevated in obese patients and declines with weight loss. Studies have demonstrated that TNF-alpha suppresses insulin action via its specific receptor; hence, TNF-alpha exacerbates insulin resistance. TNF-alpha produced by adipose tissues of obese patients acts as a risk factor for periodontal inflammation, and TNF-alpha produced due to periodontal inflammation may be an additional important factor influencing insulin sensitivity in both obese and Type II diabetes patients. This interaction is a possible mechanism accounting for the two-way relationship between Type II diabetes and periodontal disease (Nishimura and Murayama 2001; Nishimura et al. 2003).

1.1.10 The risk factors for periodontal disease: Atherosclerosis

Atherosclerosis is a progressive disease involving large-to-medium-size muscular and large elastic arteries. The advanced lesion or atheroma consists of elevated focal intimal plaques with a necrotic central core containing lysed cells, cholesterol ether crystals, lipid-laden foam cells, and surface plasma proteins including fibrin and fibrinogen. The presence of an atheroma provides a surface for enhanced platelet aggregation and thrombus formation. According to data compiled by the American Heart Association, nearly one of every two Americans dies of cardiovascular disease that is attributed to complications of atherosclerosis manifested as coronary thrombosis and myocardial infarction (Kuller 1988; Consigny 1995).

Periodontitis patients and coronary heart disease patients have a number of common characteristics, including variables such as age (positive correlation), education (negative association), gender (males higher), finances (negative association), tobacco use (positive correlation), alcohol use (positive correlation), hypertension (positive association), stress (positive association), and social isolation (positive association). Many studies have suggested a relationship between periodontitis and heart disease (Genco 2002). It is believed that, once established, periodontitis provides a biological burden of endotoxin (lipopolysaccharide) and inflammatory cytokines (especially IL-lß, PGE2, and TNF-a) which initiate and exacerbate atherogenesis and thromboembolic events.

Odds ratios comparing systemic or periodontal bone loss and coronary heart disease, adjusted for age and other established cardiac risk factors, are reported to be 1.4 for all coronary heart diseases; 1.6 for fatal coronary heart disease; and 2.0 for stroke. Major research endeavours [the *Oral Infections and Vascular Disease Epidemiology Study* (Desvarieux and others 2003) and the *Atherosclerosis Risk in Communities Study* (Beck and others from the University of North Carolina 2001; Slade and others 2003)] are currently underway that will ultimately improve our understanding of the relationship between

periodontal disease and cardiovascular disease. The relationship of periodontal disease to cardiovascular disease was also the subject of a symposium by the American Dental Association in 2001 (Ciancio 2002).

1.1.11 The risk factors for periodontal disease: Osteoporosis

Osteopenia is a reduction in bone mass due to an imbalance between bone resorption and formation, favoring resorption, and resulting in demineralization of bone and osteoporosis. *Osteoporosis* is a disease characterized by a low bone mass and fragility and a consequent increase in the risk for fracture (Wactawski-Wende et al. 1996). *Periodontal disease* is characterized by resorption of alveolar bone and loss of connective tissue attachment. The bacterial etiology of periodontal disease is well established; however, loss of oral bone may be important in the creation of a susceptible host. The strongest associations between osteopenia and periodontal disease are found when evaluating hard-tissue measurements, such as bone mineral density, and measures of loss of oral bone, such as alveolar crest height, residual ridge resorption, and tooth loss (Jeffcoat 1998). Women with osteoporosis demonstrate greater attachment loss and reduced bone density in the mandible. Measurements of mandibular bone density appear to correlate well with systemic bone density.

Weyant and others in 1999, in a cross-sectional study, assessed the association between systemic bone mineral density and the clinical measurement of attachment loss in a group of 292 elderly dentate women with a mean age of 75.5 years. The results showed that, after controlling for age, smoking, and the number of remaining teeth, no statistically significant associations were disclosed between five indicators of periodontal disease and systemic bone mineral density.

Tezal and Wactawski-Wende in 2000 examined seventy postmenopausal Caucasian women with a mean age of 62 years, and found a significant association between interproximal alveolar bone loss and systemic bone mineral density. However, their data also showed a weak and statistically *insignificant* association between clinical attachment loss and systemic bone mineral density.

As we have already established, osteoporosis and periodontitis affect a large portion of the population. It has been hypothesized that osteoporotic persons are at increased risk for developing periodontitis. The role of osteoporosis in the etiology of periodontal disease is not fully understood. In some patients, there is a correlation between a decrease of mandibular bone mass and tooth loss (Mattson 2002). While some reports suggest the lack of a significant association between periodontitis and systemic bone mass (Chestnut 2001), most observational studies support the possible role of low skeletal bone mineral density as a risk indicator for periodontitis (Jeffcoat 1998 and 2000; Reddy 2002; Tezal 2000; Wactawski-Wende and others 1996; Elders 1992). Ronderos (2000), analyzing the NHANES III data, found that in women with high dental calculus scores, the mean clinical attachment loss per person

was higher in women with low compared to normal femoral bone mineral density. Meanwhile, no difference was found when the same comparison was made in women with low or moderate calculus scores. The clear interaction between calculus and bone mineral density suggests that, in the presence of the local irritant (the calculus), osteoporosis and, to a lesser extent, osteopenia, increase the risk for periodontitis present among osteoporotic and osteopenic persons, and that this risk may be prevented or attenuated by frequent calculus removal. Further (speaking to the risk factor next under discussion), Ronderos found that postmenopausal women who reported having used estrogen replacement therapy had significantly less attachment loss than those who had never used estrogen.

As we pointed out earlier, since alveolar bone loss is a prominent feature of periodontal disease, disturbances in bone metabolism density (BMD), especially in the jaws, are suspected of being an aggravating factor in the case of periodontal disease (Wactawski-Wende *et al.* 1996).

1.1.12 The risk factors for periodontal disease: Hormone replacement therapy

Since estrogen depletion is an important risk factor for the development of osteoporosis, it is critical to consider the role of estrogen as a possible underlying cause for the association between periodontitis and low skeletal bone mineral density (Pacifici 1996). In postmenopausal women, estrogen supplementation prevents loss of skeletal and alveolar bone mineral density and may be protective against gingival inflammation (Reinhardt *et al.* 1999) and attachment loss. The effect of steroid hormones as metabolic mediators on the expression of cytokines may be a plausible explanation for the protective effect of estrogen supplementation against bone loss, infectious disease, and periodontitis (Pacifici 1996; Reinhardt *et al.* 1999). It is possible that hormone replacement therapy, calcium, Vitamin D supplementation, and other medications used to prevent low bone density have positive effects on the outcome of periodontal therapy (Orwoll *et al.* 1990; Simon 2002; Streckfus *et al.* 1997).

The sum of these studies suggests that women with osteoporosis and poor oral hygiene are at a higher risk for attachment loss than women without osteoporosis, or osteoporotic women with good oral hygiene. Further, the data suggest that this general risk may be attenuated by the use of estrogen replacement therapy. However, given the reported risks of estrogen replacement therapy to other body systems, and the fact that the magnitude of the increase in risk is not established, without further longitudinal research it is not possible to justify intervention with hormone replacement therapy for the purpose of modulating tooth attachment loss (Albandar 2002).

1.2 THE EPIDEMIOLOGY AND ETIOLOGY OF OSTEOPOROSIS, AND THE RELATIONSHIP BETWEEN SYSTEMIC BONE MINERAL DENSITY AND ORAL BONE MINERAL DENSITY

1.2.1 Epidemiology of osteoporosis: Prevalence and incidence

Osteoporosis, or porous bone, is characterized by reduced bone mass and structural deterioration of bone tissue, leading to abnormal bone architecture, fragility of bone, and increased risk of fragility fracture, particularly of the hip, spine, and wrist. Osteoporosis is a major public health threat for 44 million Americans, and approximately 1.5 million will suffer fragility fractures each year, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites. Ten million Americans already have osteoporosis, and 34 million more have low bone mass, placing them at risk for osteoporosis. Half of all women and one-quarter of men over 50 will have an osteoporosis-related bone fracture in their lifetimes.

The incidence of osteoporosis is estimated at twenty (20) percent of postmenopausal white women (Cummings and Melton 2002). An alternative approach to taking bone mass measurements is to use morphological deformities as the variable to define osteoporosis. When using defined vertebral deformities as the delimiting variable, the prevalence of osteoporosis fell to an average 12 percent in both men and women. Among women, rates ranged from five percent at age 50-54 years and rose to 18 percent at age 75-79 years (Cummings and Melton 2002). Among men the reported incidence of osteoporosis was 10 percent at age 50-54 years, rising to 18 percent at age 75-79 years. Furthermore, the already-high prevalence of this silent disease is on the rise. Projections indicate a three-fold increase in osteoporosis hip fracture in men within ten years (Cummings and Melton 2002). The likelihood of suffering a hip fracture accelerates in the ten years following the menopause in women and takes off similarly after age 70 in men.

Osteoporosis in men also has profound clinical implications (Seeman 1983, 1995, 1997). Osteoporosis is a significant health problem and contributor to disability and premature mortality among older men. Osteoporosis occurring in middle-aged and elderly men is commonly associated with alcohol abuse, smoking, immobilization, and medications. The incidence of hip fracture increases dramatically with age in both men and women, but the impact of hip fracture on mortality may actually be greater in men (Kenny Taxel 2000; Kenny Joseph Taxel 2003; Seeman) such that the number of fractures in men is nearing that observed several decades ago in women. Men suffer one-third of all hip fractures due to osteoporosis. More than two million American men suffer from osteoporosis, and millions more are at risk. Each year, 80,000 men suffer a hip fracture (among 300,000 reported annually) and one-third of

these men die within a year. Estimated national direct expenditures (hospitals and nursing homes) for osteoporosis and related fractures are $14 billion each year; men comprise one-third of all osteoporosis cases, and account for one-third of the national health care expense deriving from osteoporosis care.

1.2.2 Etiology of osteoporosis

Osteoporosis is characterized by low bone mass and micro-architectural deterioration with a consequent increase in bone fragility and susceptibility to fracture. According to the United Nations' World Health Organization (Kanis 2002), osteoporosis is operationally defined when bone mineral density (BMD) is 2.5 standard deviations (SD) or more below that which is the standard in the young normal individual. *Osteopenia* is defined as bone density levels between 1 SD and 2.5 SD below normal BMD (same; also Ahmed 1997)

Bone is a living, growing tissue. It is made mostly of collagen, a protein that provides a soft framework, and calcium phosphate, a mineral that adds strength and hardens the framework. This combination of collagen and calcium makes bones strong, yet flexible to withstand stress. More than 99 percent of the body's calcium is contained in the bones and teeth. The remaining one percent is found in the blood. Throughout one's lifetime, old bone is removed (resorption) and new bone is added to the skeleton (formation). During childhood and teenage years, new bone is added faster than old bone is removed. As a result, bones become larger, heavier, and denser. Bone formation continues at a pace faster than resorption until peak bone mass (maximum bone density and strength) is reached around age 30. After age 30, bone resorption slowly begins to exceed bone formation.

Osteoporosis develops when bone resorption and bone formation become uncoupled---that is, when rates of bone resorption exceed rates of bone formation. The bone mass attained during childhood is perhaps the most important determinant of life-long skeletal health. Achieving optimum bone mass early in life reduces the impact of bone loss related to aging. Genetic factors exert a strong influence upon peak bone mass, but controllable environmental and lifestyle factors also play a role. These include good nutrition, particularly adequate calcium and vitamin intake. Only ten percent of girls and 25 percent of boys between ages nine and seventeen obtain an adequate amount of calcium in their diet through the consumption of dairy products and vegetables. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Osteoporosis is more likely to develop if one did not reach optimal bone mass during the bone building years.

1.2.3 Etiology of osteoporosis: Detection

Osteoporosis is called the *silent disease* because bone loss occurs without symptoms. In fact, clinicians recognize *no* symptoms, except possibly back pain from a vertebral fracture. The bones become so weak that a sudden strain, bump, or fall causes a hip to fracture or a vertebra to collapse; a simple fall or lifting a heavy object may cause a vertebral fracture. It is collapsed vertebra that may initially be felt or seen in the form of severe back pain, loss of height, or spinal deformities such as *kyphosis* [literally, humpbacked], defined as abnormal backward curvature of the spine.

There have been dramatic advances in methods to diagnose osteoporosis and assess the risk of future fractures. Technology is now available to determine bone mass (or density) safely, conveniently, and at a relatively low cost in appendicular and axial skeletal sites with an accuracy exceeding 95 percent and a precision error less than one percent. Single photon absorptiometry (SPA) and single x-ray absorptiometry (SXA) are applicable to peripheral appendicular bones; dual x-ray absorptiometry (DXA) has largely replaced dual photon absorptiometry (DPA) as the optimum method to estimate axial, proximal appendicular, and total body mass. Quantitative computed tomography (QCT) has been adapted to bone densitometry, but limited accessibility and high cost have precluded the widespread routine use of quantitative computed tomography. Less expensive methods such as ultrasound, x-ray photodensitometry, and others remain to be validated in careful clinical studies. These clinical measurement methods used to assess bone mineral density are summarized in Table 1.2, on the next page.

Substantial evidence from prospective studies indicates that bone mass measurement is the most accurate available predictor of fracture risk (Black 2000). Measuring any site is probably equally predictive of the risk of all osteoporotic fractures, while measurement of the hip appears to be a better predictor of the risk of hip fracture (Delmas 2002).

Bone mineral density (BMD) tests measure bone density in the spine, wrist, or hip (the most common sites of fractures due to osteoporosis), while others measure bone in the heel or hand. These tests are painless, noninvasive, and safe. Bone density tests can detect low bone density before a fracture occurs; characterize the bone loss after a fracture has occurred; predict the individual's likelihood of fracturing in the future; and determine the individual's rate of bone loss, or monitor the effects of treatment, if the test is conducted comparatively with baseline data (Jeffcoat 1998; Jeffcoat Lewis Reddy Wang 2000).

Table 1.2. Clinical measurement methods to assess bone mineral density

Method	Sites	Units
Single photon absorptiometry	Peripheral due to need for water bath	**Bone mineral content** *g/cm* g/cm^2
Dual energy X-ray absorption	**Central or peripheral**	**Bone mineral density** areal density g/cm^2 **Bone mineral content** *in grams* refers to scanned area **Bone mineral apparent density** *g* per approximation of volume
Quantitative computed tomography	Central or peripheral	**Apparent bone density** mg/cm^2

1.2.4 Risk factors for osteoporosis

Risk factors for osteoporosis can be divided into *non-modifiable* and *modifiable* risk factors. The non-modifiable risk factors are gender (2:1 female to male); age (bones becomes less dense and weaker with age); early menopause; small or thin body frame; ethnicity (Caucasian and Asian women are at highest risk; African-American and Latino women have a lower but significant risk); and family history (people whose parents have a history of fractures also seem to have reduced bone mass and may be at risk for fractures) (Cummings Nevitt Browner 1995; Cummings and Melton 2003).

Risk factors that individuals *can* change are a lifetime diet lacking in calcium and Vitamin D; a lack of exercise, an inactive lifestyle, or extended bedrest; cigarette smoking and the excessive use of alcohol; anorexia; and levels of sex hormones off the norm [an abnormal absence of menstrual periods (amenorrhea), low estrogen level (menopause), and low testosterone level in men]. Low bone mass, certain medications (glucocorticoids or some anticonvulsants), the propensity to fall, and the presence of systemic disease such as hypothyroidism are modifiable to some extent (Cummings Nevitt Browner 1995; Cummings and Melton 2003).

Large cross sectional studies have found a strong inverse relation between bone mass and age. Results of early prospective studies of forearm bone loss in women suggested that the rate of bone loss decreases with increasing age. More recently, several longitudinal studies indicated that bone loss accelerates about 0.4-1.3 percent per year in the peripheral skeleton of men and women up to age 80 (Greenspan Dresner-Pollak Parker London Ferguson 1997; Heyse 1993).

Osteoporosis research has historically been focused on the disease in postmenopausal women. Although osteoporosis is less common in older men, the disease nonetheless represents a major health concern for men (*above*). The reason for the rising incidence of osteoporosis fractures in men is unclear, but the extension of the actual human life span, improvements in the quality of a long-lived-life, and better management of other chronic disease most likely play a role. At the present time, men over 50 years of age have a 19-25 percent lifelong risk of any osteoporotic fracture (Seeman Melton O'Fallon Riggs 1983; other Seeman 1995, 1997, 2001). Testosterone is thought to be important in the development of peak bone mass but its role in age-related bone loss is not established.

1.2.5 Risk factors for osteoporosis: Vitamin D deficiency

Vitamin D intake is essential for maintenance of the skeleton throughout the lifespan, and often it is compromised in the elderly. Vitamin D is also derived from the conversion of precursors in the skin that are stimulated by sunlight. Decreased mobility and avoidance of the sun contribute to Vitamin D deficiency in the elderly. The skeletal effects of Vitamin D are two-fold: the vitamin ensures mineralization of the organic matrix of bone and the vitamin mediates mobilization of stored calcium and phosphate from bone to blood to achieve mineral homeostasis. Inadequate levels of Vitamin D produce a secondary increase in the release of parathyroid hormone that stimulates bone resorption and can result in osteoporosis (Simon LeBoff Wright Glowacki 2002).

1.2.6 The relationship between systemic bone mineral density [BMD] and oral bone mineral density [BMD]

Studies discussing the relationship between systemic bone mineral density (BMD) and oral bone mineral density (BMD) are summarized in Table 1.3. Most studies reported to date concerning this relationship are cross-sectional, using different populations and different methods to assess bone mineral density.

Kribbs and colleagues (1990, 1989, 1983, and Table 1.2) were the first to study the relationship between systemic bone mineral density and oral bone mineral density in both normal and osteoporotic women. Assessments of total body calcium were taken by neutron activation analysis, and found to be associated with mandibular density as measured by quantitative analysis of intra-oral radiographs. In a comparison of 85 individuals in two groups, the osteoporotic group had 20 percent less mandibular bone mass and density and a thinner cortex at the gonion than the normal group. The osteoporotic group also had a greater percentage of subjects who were edentulous.

Von Wowern and colleagues (1994) found less mandibular bone mineral content as measured by dual photon absorptiometry than in fourteen normal women. Streckfus and colleagues (1997) used quantitative measurements of vertical bitewing and hand radiographs in patients with active periodontitis.

The radiographs showed postmenopausal women on estrogen therapy had more alveolar bone loss, more missing teeth, and reduced alveolar and second metacarpal bone density than pre-menopausal women. Shrout and colleagues (2000) used morphologic measurements from digitized images of bitewing radiographs to correlate with lumbar and femoral bone mineral density in 45 post menopausal women who had no or only mild periodontal disease (no probing depths >5 mm). The complexity of the pattern of the trabecular bone weakly correlated with lumbar spine and femoral bone mineral density.

Most studies relate systemic bone mineral density with mandibular mineral density. In one study of both maxilla and the mandible (Southard 1992), forty-one dentate Caucasian women ages 20-78 were evaluated using quantitative intraoral radiography and systemic bone densities determined by dual energy x-ray absorptiometry (DXA). The density of maxillary alveolar process bone was significantly related to the density of the mandibular alveolar process, lumbar spine, hip, and radius in healthy women. The results also indicated that maxillary alveolar process bone density declined with age.

In a preliminary report of the oral ancillary study of the Women's Health Initiative, 158 patients with a mean age of 62.2 years were evaluated (Jeffcoat 1998). Hip bone mineral density was measured by dual energy x-ray absorptiometry (DXA) and mandibular bone density by quantitative digital intraoral radiography. A significant correlation was found between mandibular basal bone and hipbone mineral density.

In summary, the collective data reported in most of these cross-sectional studies appears to indicate a relationship between systemic bone mineral density and oral bone mineral density, but the sample size on all of these studies was very small and only one investigator (Jeffcoat 1998) adjusted for age. Generally, most researchers used differing populations and did not adjust for the other co-variants such as smoking. The exception to this is Kribbs, studying both normal and osteoporotic women (1990), who showed 20 percent less mandibular density as measured by quantitative analysis of intra-oral radiographs. Additional data from ongoing longitudinal studies will further elaborate this relationship.

All of the research discussed above and others is summarized in Table 1.3, next.

Table 1.3 Relationship between systemic bone mineral density (BMD) and oral bone mineral density (BMD)

Authors	Population	Major Result	Type of study
Jeffcoat *et al.*	158 postmenopausal women, ages 62.2±7.6 years	Significant correlation between hip BMD and mandibular-basal BMD	Cross-sectional
Shrout *et al.*	45 postmenopausal women with no or mild periodontitis. Mean age 57.4 ± 5.8	Complexity of the trabecular pattern weakly correlated with lumbar spine and femoral BMD	Cross-sectional
Southard *et al.*	41 dentate Caucasian women, ages 20 to 78 years	Significant correlation between the density of maxillary and mandibular alveolar process, lumbar spine, hip, and radius in healthy women.	Cross-sectional
Streckfus *et al.*	28 healthy women, ages 23-78	Strong correlation between alveolar bone and the second metacarpal densities. Both reduced in post-menopausal women.	Cross-sectional
Jacobs *et al.*	69 women receiving HRT, aged 32-64 at entry	Correlation between spinal density and mandibular bone mass at the second examination (average follow-up 5.1 years)	Cross-sectional
von Wowern *et al.*	12 women with osteoporotic fractures	Osteoporotic subjects had less bone mineral content	Cross-sectional
Kribbs	85 osteoporotic women and 27 normal women, ages 50-85	Osteoporotic group had less mandibular bone mass and density	Cross-sectional
Kribbs	85 osteoporotic women	Total body calcium, bone mass at radius, and bone density at spine correlated with mandibular mass	Cross-sectional
Kribbs *et al.*	50 normal women ages 20-90	Mandibular bone mass correlated with bone mass at spine and wrist	Cross-sectional
Kribbs *et al.*	30 postmenopausal women	Total bone calcium associated with mandibular bone density	Cross-sectional
Famili *et al.*	398 dentate women (average age 75.5 years)	Statistically significant relation between tooth loss and systemic BMD	Cross-sectional

1.2.7 The relationship of periodontal disease and osteoporosis

The relationship of tooth loss to bone mineral density has been studied. Several reports find a correlation between tooth losses and diminished systemic bone mineral density. Several mostly cross-sectional reports have used a variety of parameters to evaluate periodontal disease severity in subjects with decreased bone mineral density. These reports are summarized in Table 1.4, which examines the relationship of periodontal destruction and bone mineral density (BMD). The previous Table 1.3 examined the relationship between systemic bone mineral density (BMD) and oral bone mineral density (BMD). The next table, Table 1.4, examines the relationship between periodontal destruction and bone mineral density.

Table 1.4 Relationship of periodontal destruction and bone mineral density (BMD)

Authors	Population	Major Result	Type of study
Lundstron *et al.*	15 women with osteoporosis, 21 women with normal BMD	No statistically significant differences in gingival bleeding, probing pocket depths, gingival recession, and marginal bone level	Cross-sectional
Taxel *et al.*	70 postmenopausal Caucasian women aged 51-78	Mean ABL significantly correlated with BMD	Cross-sectional
Weyant *et al.*	292 dentate women (average age 75.5 years)	No statistically significant relation between periodontal disease and systemic BMD	Cross-sectional
Payne	Female periodontal maintenance patients within five years of menopause; 21 with normal BMD and 17 osteoporotic women	Greater ABL, crestal and subcrestal density bone loss in the osteoporotic and estrogen-deficient women	2-year longitudinal clinical study
Reinhardt *et al.*	Women within five years of menopause, 59 with adult periodontitis and 16 non-periodontitis. Stratified by serum estradiol levels	Non-smoking osteopenic/ osteoporotic periodontitis patients with estrogen deficiency had more bleeding on probing and clinical attachment levels	2-year prospective longitudinal study
Hildebolt *et al.*	135 postmenopausal women aged 41-70 years, no moderate or severe periodontitis	Attachment loss was correlated with tooth loss but not with BMD	Cross-sectional
Streckfus *et al.*	28 healthy women, ages 23-78	More ABL, more missing teeth, in postmenopausal women on estrogen therapy than in premenopausal women	Cross-sectional
von Wowern *et al.* .	12 women with osteoporotic fractures	Osteoporotic subjects had more loss of attachment than normal subjects	Cross-sectional
Elders *et al.*	216 females between 46 and 55	No significant correlation was observed between probing depth, bleeding on probing, missing teeth, alveolar bone height, and bone mass	Cross-sectional

In the research by Elders and colleagues (1992), lumbar bone mineral density and metacarpal cortical thickness were compared to alveolar bone height measured on bitewing radiographs, and to clinical parameters of periodontitis. No significant relationship was observed between the bone mass measurements and alveolar bone height, or the periodontal parameters. The mean age in this group was relatively young, between 46 and 55 years of age, and the sample size was very small, which could have contributed to the lack of correlation. Similar findings were reported in a study of tooth loss and attachment loss when related to vertebral and proximal femoral bone mineral density. One-hundred-thirty-five (135) women with at least ten teeth and no evidence of moderate or severe periodontal disease were examined. Attachment loss correlated with tooth loss but not with vertebral or proximal femur bone density (Looker1997). In an age cohort of 70-year-old women, fifteen subjects with osteoporosis were compared to twenty-one subjects with normal bone mineral density. No statistically significant

differences were found in gingival recession or marginal bone level between the women with osteoporosis and the women with normal bone mineral density (Jeffcoat 2001).

In contrast to these reports, other authors have noted a significant relationship between systemic osteopenia and periodontal bone loss. Von Wowern and colleagues (1994) found greater amounts of loss of attachment in osteoporotic women, in a small population with a mean age of 68. Osteoporosis was assessed using the bone mineral content of the mandible and forearm determined by dual photon scanning.

In a two-year longitudinal clinical study, alveolar bone height and bone mass density changes were studied in seventeen osteoporotic/osteopenic women, compared with twenty-one women with normal lumbar spine bone mineral density. Osteoporotic women exhibited a higher frequency of alveolar bone height loss and crestal and subcrestal density loss relative to women with normal bone mineral density (Payne 1999).

Fifty-nine moderate/advanced adult periodontitis patients and sixteen non-periodontitis subjects, all within five years after menopause at baseline, were stratified based on serum estradiol levels. Attachment loss was assessed over a two-year period and correlated to bone mineral density and serum estradiol levels. Serum estradiol levels did not influence the percentage of sites losing attachment for either the periodontitis or the non-periodontitis groups. The estradiol-deficient group had a trend toward a higher frequency of sites with attachment loss>2 mm. Larger prospective longitudinal studies are needed to further evaluate osteoporosis as a risk factor for periodontal disease (Reinhardt *et al.* 1999).

Research conducted by the author and colleagues (Famili *et al.* 2005) concluded that there was little evidence of an association between periodontal disease and longitudinal changes in bone mineral density, but there was significant association between tooth loss and change in bone mineral density.

Cross-sectional studies have limitations. No information relevant to the diseases studied is available prior to the date of the exam. Although both osteopenia and periodontal disease are chronic diseases and can be assumed to have been present prior to the observations, most of the studies adjust only for age and do not consider other risk factors. Another common deficiency among these studies is that the sample size is usually too small to make definite associations between periodontal disease and osteoporosis as measured by using bone mineral density.

1.3 THE RELATIONSHIPS AMONG OSTEOPOROSIS, BONE LOSS, AND PERIODONTAL DISEASE IN MEN GENERALLY AND IN MEN WITH PROSTATE CANCER UNDER ANDROGEN DEPRIVATION THERAPY

1.3.1 Osteoporosis in men

Bone loss occurs more gradually and at a later age in men with idiopathic age-related bone loss. This speaks directly to the issues of our current research, and in Table 1.5 we outline the published cross-sectional and longitudinal studies performed in men with prostate carcinoma who were treated with androgen deprivation therapy. These men, on average, have bone mineral density measurements that are 6.5-17.3 percent lower when compared with bone mineral density measurements in eugonadal men who are treated without androgen blockade. The duration of androgen deprivation therapy affects bone mineral density values significantly. In longitudinal studies, a 5.7-8.5 percent decrease in lumbar spine cancellous bone mineral density was revealed (using QCT) and a 1.8-2.3 percent decrease in femoral neck bone mineral density (using DXA) was recorded after twelve months of androgen deprivation therapy.

Men with prostate carcinoma who are treated with androgen deprivation therapy are elderly and are at risk for a wide variety of metabolic bone problems. Although some increase in the rate of bone loss may occur after the age of 50 years, this increase is not as rapid as that observed in women around the time of menopause (Warming 2002). Longitudinal studies have shown the rate of cortical bone loss in men to be approximately 0.5 percent to 1 percent per year in later life (Seeman 1995). The loss of cancellous bone, on the other hand, tends to proceed more rapidly (Mazess 1982 and 1990), which is reflected in an increasing incidence of spine and hip fractures in elderly men, particularly after the age of 75 years (again, Seeman 1995, 1997, 2001).

Data on bone loss in otherwise healthy elderly men is sparse. Even less information is available concerning bone loss, fracture and mortality in men with additional risk factors for bone loss. Peak bone mass is higher in men than women because men have bigger bones. Peak bone mineral density is the same (Seeman 1997). The amount of trabecular bone lost at the spine and iliac crest during aging is similar in men and women. Cortical bone loss is less in men because endocortical resorption is less and periosteal formation is greater. Bone fragility is less in men because the cross-sectional surface of the bone is larger; because trabecular bone loss is less as a percentage of the higher peak bone mass; because trabecular bone loss occurs by thinning rather than perforation; and because periosteal appositional growth compensates for endocortical resorption by maintaining the bending strength of bone (again, Seeman).

[Seeman (1999) even is capable of presenting data regarding racial differences in the fragility of bone, in addition to gender differences in fragility. Blacks have shorter vertebrae than whites, but vertebral width is similar. Trabecular thickness is greater in blacks than whites. Men have wider long bones than women. Blacks have wider long bones than whites. He summarizes the issue by saying that racial differences in vertebral strength are likely to be bone mineral density-, not size-, dependent. Greater periosteal expansion during growth in males than females, and in blacks than whites, establishes the gender and racial differences in peak bone size.]

The higher mortality rate (one-third greater) associated with hip fracture in men (Seeman 1995) compared with women may in fact be due to the frequent presence of underlying medical conditions or risk factors, such as a slow decrease in serum-free testosterone, alcoholism, tobacco use, hypogonadism, and disorders of calcium and Vitamin D absorption or metabolism. In one case control study, approximately a third of the men studied had a significant underlying condition that could affect calcium or bone metabolism (Seeman 1995, 2001; Deng 2004). Seeman (1997) sums up the risk factors for fracture in men by citing the age-related decline in testosterone, adrenal androgens, growth hormone, and insulin-like growth factor 1. Men with vertebral fractures often have hypogonadism or other illnesses with what Seeman calls *suspiciously few clinical features*---alcoholism, myeloma, malabsorption, primary hyperparathyroidism, haemochromatosis, and Cushing's disease.

[In 2004, conceding that *the single most important consideration in the treatment of osteoporosis is the individual's absolute risk of fracture,* Seeman considered what was out there that worked in the treatment of osteoporosis. Reported to reduce vertebral fractures are the bisphosphonates, raloxifene, parathyroid hormone, and strontium ranelate. The bisphophanates and hormone replacement therapy have been used to reduce fractures in one population of women, but hormone replacement is clearly not recommended (the discussion above). Calcium plus Vitamin D and the mechanical device of hip protectors reduced fractures in one study of the institutionalized elderly. Seeman saw little evidence to support treatment with calcitonin, fluoride, anabolic steroids, or active Vitamin D metabolites, and could only recommend lifestyle changes to maintain lifetime bone strength, not statistically reduce fracture risk.]

1.3.2 Bone loss in men with prostate cancer

There has been a gradual increase in the incidence of prostate cancer around the world since the 1960s. Prostate cancer occurs in older men and, as previously mentioned, aging is associated with bone loss in the range of 0.5 percent to 1 percent per year (Higano 2003, Mazess 1982). Decreased testosterone levels and hypovitaminosis D also occur in this population (Simon 2002, Higano 2003). These factors may help explain why osteopenia may be present in 10 percent to 25 percent of men with prostate cancer even

before androgen deprivation therapy is begun. While androgen deprivation therapy is an effective measure to control advanced prostate cancer, the development of osteoporosis in patients treated with androgen deprivation therapy has not aroused general attention until recent years (Wei *et al.* 1999; Diamond 1998; Morote *et al.* 2003; Deng 2004). Ross and Small indicated very recently (2002) that osteoporosis was an important and debilitating side effect of androgen deprivation therapy, but the precise estimates of its incidence and importance have not yet been made fully clear.

1.3.3 Osteoporosis in men with prostate carcinoma under androgen suppression therapy

**The literature regarding this subject is summarized as Table 1.5, below.*

Prostate carcinoma is the most common visceral malignancy and the second leading cause of death from cancer in men (Greenlee 2001). Androgen deprivation therapy is the recommended treatment for men with metastatic or locally advanced, non-metastatic prostate carcinoma (Stoch *et al*. 2001). Although it has been demonstrated that this form of therapy significantly reduces tumor growth and improves survival beyond three years after completion of the androgen deprivation therapy, there is growing concern regarding the negative effects of androgen deprivation therapy on the skeleton. Accelerated bone loss (Higano 2003), osteoporosis, and a potential for increased fracture rates have been reported in men with prostate carcinoma who are receiving androgen deprivation therapy. Because many patients who present with prostate carcinoma are elderly and may have pre-existing osteoporosis, sub-clinical Vitamin D deficiency, or any of a multitude of medical problems, the risk of skeletal deterioration is increased (Simon 2002). At present the prevalence of osteoporosis in men under androgen suppression is not well known, and neither is the impact of the time spent under this treatment.

Table 1.5 Percent change in lumbar spine and hip bone mineral density (BMD) in men with prostate carcinoma receiving androgen-deprivation therapy

			Percent change in BMD per year		
Study	**Number of Patients**	**Treatment**	**LS DXA**	**LS QCT**	**Hip DXA**
Mallefert1999	12	LHRH agonist	-4.6	_	-3.9
Daniell 2000	16	Orchiectomy/LHRH agonist	_	_	-2.4
Higano1999	18	CAB	-4.5	-	-2.5
Diamond 1998	12	CAB	_	-6.6	-6.5
Smith 2001	21	CAB	-3.3	-8.5	-1.8
Diamond 2001	21	CAB	_	-5.7	-2.3
Smith 2003	51	LHRH agonist/ CAB	-2.2	_	-2.8
Mittan 2002	15	CAB	-2.8	_	-3.3
Berruti 2002	42	LHRH	-2.3	_	-0.5

Footnote:
Table 1.5 outlines the published cross-sectional and longitudinal studies performed in men with prostate carcinoma who were treated with androgen deprivation therapy (ADT). On average, these men have BMD measurement that are 6.5-17.3% lower compared with BMD measurement in eugonadal men who are treated with androgen blockade. The duration of ADT affects BMD values significantly. In longitudinal studies, a 5.7-8.5% decrease in lumbar spine cancellous bone mineral density was shown (using QCT) and 1.8-2.3% decrease in femoral neck BMD.

1.4 THE RELATIONSHIP OF PERIODONTAL DISEASE IN MEN WITH PROSTATE CANCER UNDER ANDROGEN DEPRIVATION THERAPY. A BRIEF SUMMARY PREFACE TO THE SUBSEQUENT CHAPTERS

The relation of periodontal disease and osteoporosis due to androgen ablution is not well established. Studies to evaluate the relationship between osteoporosis due to androgen deprivation therapy and periodontal disease are essential for enhancing our understanding of systemic bone pathogenesis. There is no literature on the association between periodontal disease and prostate cancer under androgen deprivation therapy.

To address whether the two diseases are linked, we will analyze two data sets. In the first analysis, we will test the hypothesis that older women with periodontal disease will experience faster rates of bone loss *(Chapter Two).*

The second analysis will involve men undergoing androgen deprivation therapy for prostate cancer. These men have been enrolled in *Bone loss in men with prostate cancer treated with androgen deprivation therapy* (Susan L. Greenspan, MD, principal investigator), which is testing the hypotheses (1) that androgen deprivation therapy in men with prostate cancer is associated with a rapid increase in bone resorption and bone loss, as well as a change in body composition; and (2) that androgen deprivation in men with advanced prostate cancer therapy is associated with progressive loss of bone and lean body mass compared to normal controls; and (3) that bone resorption, bone loss, and general bone health will be further altered by additional systemic or local therapy for prostate cancer. As part of the current research, we will add a periodontal assessment and will test the additional hypothesis (4) that men with prostate cancer undergoing androgen deprivation therapy with have a higher prevalence of periodontal disease (*Chapter Three*).

Finally, we will examine the correlation between measures of bone mineral density and bone turnover to the existence of periodontal disease in this population of older men *(again, Chapter Three).*

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2.0 CHAPTER TWO

LONGITUDINAL STUDY OF PERIODONTAL DISEASE AND EDENTULISM WITH RATES OF BONE LOSS IN OLDER WOMEN

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Published in the *Journal of Periodontology* 76:11-15, January 2005.

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2.1 Abstract of the research

Purpose: Previous cross-sectional studies have suggested a link between periodontal disease and osteoporosis. The purpose of the present study is to evaluate the association between changes in bone mineral density (BMD) and clinical signs of periodontal tissue destruction and tooth loss over a two-year period**.**

Methods: A total of 398 women (mean age 75.5 years) were randomly selected for an ancillary study of periodontal disease. We evaluated osteoporosis in association with the presence or absence of teeth, and further evaluated osteoporosis in association with periodontal disease. All subjects were participants at the Pittsburgh Clinical Center for the Study of Osteoporotic Fractures (SOF), a prospective cohort study of women 65 years+ designed to determine risk factors for fractures. Oral health examinations, including periodontal probing and attachment loss, were performed at the fourth clinical visit, on average six years after baseline. BMD of the total hip and its sub-regions were measured using dual energy X-ray absorptiometry at the time of dental examination, and two years later. Results are expressed as annual percentage change.

Data analysis: Generalized linear models were used to assess the association between BMD and the presence or absence of teeth and periodontal health status. Periodontal variables among dentate women included average loss of periodontal attachment (LOA); the number of sites with at least four millimeters (4mm) of attachment loss; and the presence or absence of calculus.

Results: A total of 145 (36.4 percent) women were edentulous and 163 (80.7 percent) had periodontal disease. Dentate women reported higher education ($p<0.001$), and a higher calcium intake ($p=0.002$). Absolute BMD and percentage change in BMD were similar in dentate and edentulous women. We found no difference in BMD, or in absolute or percentage change in BMD between women with or without periodontal disease.

Conclusion: Little evidence exists for an association between edentulousness, periodontal disease, and longitudinal changes in BMD.

2.2 Background and rationale for the research

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis is a major public health problem that most often affects postmenopausal women.

In the United States osteoporosis affects more than 25 million people, and predisposes patients to more than 1.3 million fractures annually (*Annals of Periodontology Consensus Report* 1996). Since alveolar bone loss is a clinical feature of periodontal disease, disturbances in bone metabolism and decreases in the bone mineral density (BMD) of the skeleton, especially in the jaws, may be a factor in periodontal disease (Wactawski-Wende *et al.* 1996). Osteoporosis and periodontal disease lead to significant morbidity, mortality, and expense.

The clinical importance of generalized bone loss as a contributor to alveolar bone loss and subsequent tooth loss is unclear. To date, the evidence for an association between tooth loss and bone mineral density (BMD) in the extra-cranial skeleton has been derived from cross-sectional studies, and results have been inconclusive (Tezal 2000). Several large studies conducted in early postmenopausal women failed to find significant associations between tooth status and BMD. Elders (1992) found no relationship between the number of missing teeth and either spine BMD or metacarpal thickness. Krall *et al.* (1996) conducted a longitudinal study on associations between tooth loss and bone loss in whole bodies, in the femoral neck, and in the spine, including 189 healthy white dentate postmenopausal women who participated in three intervention trials conducted within a seven-year period. Forty-five women (24 percent) reported having lost one or more teeth. The rates of BMD changes at all three sites (whole body, femoral neck, spine) were independent predictors of tooth loss in the multivariate models, supporting a role for systemic bone loss in the development of tooth loss among postmenopausal women.

Bando *et al.* (1998) suggested that sufficient masticatory function with periodontally healthy dentition may inhibit or delay the progress of osteoporotic changes in skeletal bone, or that edentulous women may be more susceptible to osteoporosis. The role of osteoporosis or osteopenia in the etiology of periodontal disease is not fully understood. Observational studies support the possible role of low skeletal BMD or osteoporosis as risk indicators for reduced alveolar crestal height (Wactawski-Wende *et al.* 1996). Ronderos *et al.* (2000) studied the possible association of periodontal disease with femoral bone mineral density (BMD) in a large sample of U.S. adults (n=11,655). Their finding indicates that, in the presence of high calculus scores, females with osteoporosis are at an increased risk for attachment loss.

In our earlier report (Weyant *et al.* 1999), we found no association between BMD and periodontal disease. However, no longitudinal studies have been reported to date. One intent of the present study was to extend the earlier report (Weyant *et al.* 1999) and evaluate the link between changes in bone mineral

density and clinical signs of periodontal tissue destruction. In addition, we examined the association of between edentulism and changes in BMD.

2.3 The design/setting/patients *and* the materials and methods of the research

A total of 398 women (mean age 75.5 years) were randomly selected for an ancillary study of periodontal disease, presence or absence of teeth, and osteoporosis. All subjects participated in the Pittsburgh Clinical Center for the Study of Osteoporotic Fractures (SOF), a prospective study of a cohort of elderly women >65 years of age at baseline, to determine risk factors for fractures.

From September 1986 to October 1988, a total of 2,401 women who were at least 65 years of age or older were recruited for the SOF from the Monongahela Valley near Pittsburgh, Pennsylvania. Age-eligible women were identified on voter registration lists for zip codes within a 25-mile radius of Monessen, Pennsylvania. To be eligible to participate in this ancillary study, women had to be willing to continue participation in the SOF study, willing to have a dental examination, and willing to voluntarily sign a University of Pittsburgh Institutional Review Board (IRB)-approved consent form. Exclusion criteria for this study included presence of medical conditions that would preclude conducting an adequate oral examination. All women presenting for SOF examinations when the dentist examiner was present and who met the above eligibility criteria were eligible for enrollment into the dental study.

BMD measurement

Bone mineral density (*g/cm*) of the total hip and its sub regions (the femoral neck, the inter-trochanteric region, the trochanter) was measured using dual X-ray absorptiometry with Hologic QDR-1000 scanners (Hologic Inc., Waltham, MA). Bone mineral density of the calcaneus was measured with Osteo Analyzers (Siemens-Osteon, Wahiawa, HI) using single- photon absorptiometry at the baseline examination. Details of these measurement methods and densiotometry quality control procedures have been published elsewhere (Ensrud 1995).

Periodontal assessment

The assessment for periodontal destruction was made at three sites on the buccal aspect (mesiobuccal, midbuccal, distobuccal) of all remaining natural teeth (Weyant 1999). Only fully erupted teeth were measured. Loss of attachment was defined both clinically and quantitatively as the distance in millimeters (mm) from the cementoenamel junction (CEJ) to the base of the pocket. Probing depth was the distance from the free gingival margin (FGM) to the base of the sulcus/pocket. A woman was diagnosed with periodontal disease if she had more than three millimeters (>3mm) attachment loss (Weyant *et al.* 1999).

Statistical analysis

All data were screened for accuracy and completeness. *SAS 8.2e*™ software was used to analyze the data. Descriptive statistics were calculated for all variables including means, standard deviations, ranges and

percentages. Linear regressions were used to compare the rate of bone loss in edentulous *vs*. dentate women. Among dentate women, women with attachment loss >4 mm *vs*. women with <4 mm of attachment loss on more than twelve teeth were also compared. We initially adjusted for age. Multivariate adjusted models included variables known to influence bone density and fracture outcomes (age, weight, education, dietary calcium intake, alcohol use, walking for exercise).

2.4 The results of the research, as described for this chapter

Dentate *vs*. edentulous status of 398 women in the study was examined. Most (253) or 64 percent, were dentate, and 145 (36 percent) were edentulous. Dentate women were more likely to report a higher education, greater calcium intake, drinking alcohol and a dental examination in the last two-years compared with edentulous women. There were no differences in age, body weight, smoking, hormone use, and physical activity between the two groups. Similar proportions of dentate and edentulous women reported a history of fracture or osteoporosis.

For the most part there was no difference in age-adjusted BMD, absolute rates of bone loss, or percentage rate of bone loss between dentate and edentulous women for tooth loss at other sites. Further adjustments for age, weight, education, dietary calcium intake, drinking alcohol, and walking for exercise had little effect on these results. The rate of bone loss at the trochanter was somewhat greater among edentulous women (0.86 percent per year) compared to dentate women (-0.52 percent per year).

Periodontal disease

The majority (80 percent) of dentate women had some evidence of periodontal disease (*Table 1.4*). Women with periodontal disease were slightly older than women without periodontal disease *(p*=0.07), but all other characteristics were remarkably similar in the two groups. We found no difference in BMD, or in absolute or percentage change in BMD between women with and without periodontal disease (*Table 1.4*).

We also correlated several other measures of periodontal disease with BMD, including average periodontal attachment loss, number of sites with > 6 mm attachment loss, site with > 4 mm attachment loss, average number of sites with bleeding, calculus and probing depth. In general there was no association between periodontal disease and rate of bone loss.

2.5 A discussion of the research, as described for this chapter

The overall prevalence of edentulism in this population of older women was higher (36 percent) compared with the 23 percent edentulism rate reported for the U.S. population of women ages 70 to 74 years as published in the NHANES III study. The higher prevalence observed in our study could have reflected a continued increase in edentulism with advancing age. The women in our study ranged from 73 to 84 years in age. We found little evidence to support an association between osteoporosis and edentulism.

BMD and rate of bone loss were similar in these two groups even after adjustments for established correlating factor of edentulism.

Tooth loss has been observed to be related to bone density in the oral cavity in a limited number of studies. When interpreting results in various anatomic regions, it is necessary to remember that tooth loss is highly influenced not only by periodontal disease, but also by the local practices of the dental community, as well as other factors related to oral health.

The majority (80 percent) of dentate women had some evidence of periodontal disease (p=0.07). We found no statistically significant associations between periodontal disease variables (average periodontal attachment loss, average number of sites with bleeding, and average number of sites with calculus) and BMD at trochanter, inter-trochanter and femoral neck either cross-sectionally or longitudinally. This was true even after controlling variables for age, weight, and other important correlating factors. A possible explanation of our lack of an association between periodontal disease and BMD may be because our population was chronologically older, and were missing among them a large number of teeth. We have no information on the individual reasons for missing teeth. This edentulousness could be due to periodontal disease that occurred much earlier in the individual's life.

Historical events such as tooth loss can alter the interpretation of the current status of their periodontal disease. Loss of several periodontally involved teeth can result in an improvement of periodontal summary scores such as average loss of attachment. Compared to the other NHANES III studies (Winn 1999; Slade 1999), average attachment loss for the U.S. population was reported to be 2.1 mm, while our data for our population showed an average attachment loss\ of 2.49 mm. The major strengths of this current study are its large sample size and well-controlled measurement of variables, which could confound relationship with BMD. The sample is drawn randomly from a large population of community-dwelling women.

Limitations

Interpretations of the present study may be limited, since periodontal measures of bone such as subtraction radiography or Shei bone score measurement were not available. In addition, blinded dental examiners were only able to record a single assessment of periodontal measurements.

Conclusion

There was little evidence of an association between edentulousness, clinical and periodontal disease, and longitudinal changes in BMD in this population of older women. Future studies may be needed to longitudinally correlate periodontal disease and BMD over the same period.

Table 2.1. Characteristics of postmenopausal women with teeth and without teeth (N=398)
Values are mean (SD), number (%), or median (range)

	Dentate (n= 253)	Edentulus (n= 145)	p-value
Age (yrs)	75.9 (4.12)	78.8 (4.40)	0.741
Height (cm)	158.0 (5.45)	157.3 (6.01)	0.239
Weight (kg)	68.5 (12.69)	67.85 (11.82)	0.587
BMI (kg/m^2)	27.4 (4.80)	27.4 (4.55)	0.935
Age at menopause (yrs)	47.2 (6.5)	46.8 (5.6)	0.523
Smoking (n, %)			
Past	75 (29.64)	47 (32.64)	
Current	11 (4.35)	7 (4.86)	0.503
Education (n, %)			
> 12 years	145 (57.31)	103 (71.03)	
> 16 years	91 (35.97)	12 (8.28)	<0.001
Dietary Calcium Intake (mg/day)$^{\$}$	500.82 (1.81)	411.13 (1.93)	0.002
Calcium supplement use, n (%)	103 (40.71)	49 (33.79)	0.172
Alcohol Drinking, n (%)	97 (38.49)	43 (29.66)	0.076
Walking for exercise, n (%)	111 (43.9)	46 (31.7)	0.017
Diabetes, n (%)	17 (6.72)	8 (5.52)	0.634
Osteoporosis, n (%)	25 (10.00)	12 (8.39)	0.599
History of Fracture since 50 years, n (%)	114 (45.1)	67 (46.2)	0.825
Maternal history of fracture, n (%)	53 (25.85)	23 (21.30)	0.371
Thiozide use (n, %)	14 (17.00)	22 (15.17)	0.636
Estrogen use (n, %)			
Past	46 (18.47)	24 (16.78)	
Current	18 (7.23)	8 (5.59)	0.423
Glucocorticoid use (n, %)	20 (7.91)	13 (8.97)	0.712
Dental examination (n, %)			
Less than 6 months	177 (69.86)	12 (8.28)	
One year ago	44 (17.39)	18 (12.41)	
Two years ago	12 (4.74)	23 (15.86)	
> 2 years ago	20 (7.91)	92 (63.45)	<0.001

$ = Analysis was performed log transformed variable
Values are mean (SD), number (%).

Table 2.2 Age- adjusted BMD and annualized per cent change in BMD by edentulous status

	Dentate (n=253)	Edentulous (n=145)	p-value
BMD (g/cm2)			
Total Hip	0.74 (0.01)	0.73 (0.01)	0.528
Femoral Neck	0.63 (0.01)	0.63 (0.01)	0.729
Intertrochanter	0.87 (0.01)	0.86 (0.01)	0.661
Trochanter	0.57 (0.01)	0.56 (0.01)	0.401
Absolute rate of change in BMD (mg/cm2,yr)			
Total Hip	-4.31 (0.55)	-5.07 (0.73)	0.408
Femoral Neck	-3.18 (0.57)	-3.03 (0.75)	0.871
Intertrochanter	-4.92 (0.71)	-5.88 (0.94)	0.415
Trochanter	-2.96 (0.54)	-4.60 (0.71)	0.068
Per cent rate of change in BMD (%/yr)			
Total Hip	-0.60 (0.08)	-0.72 (0.10)	0.343
Femoral Neck	-0.50 (0.09)	-0.49 (0.12)	0.958
Intertrochanter	-0.59 (0.08)	-0.72 (0.11)	0.325
Trochanter	-0.52 (0.10)	-0.86 (0.13)	0.045

Table 2.3 Characteristics of women with and without periodontal disease (n=202)

	Periodontal Disease (> 4 mm)		
	Yes (n= 163)	No (n= 39)	p-value
Age (yrs)	76.39 (4.25)	75.08 (3.67)	0.078
Height (cm)	157.65 (5.11)	158.43 (5.88)	0.407
Weight (kg)	68.01 (12.40)	69.33 (9.83)	0.539
BMI (kg/m^2)	27.37 (4.87)	27.71 (4.19)	0.690
Age at menopause (yrs)	47.83(6.03)	46.02 (7.99)	0.118
Current Smoking (n, %)	9 (5.52)	0 (0.0)	0.211
Education (n, %)			
> 12 years	97 (59.5)	21 (53.9)	0.330
> 16 years	54 (33.1)	16 (41.0)	
Dietary Calcium Intake (mg/day)	484.91(1.81)	498.66(1.78)	0.796
Alcohol Drinking, n (%)	61 (37.65)	14 (35.90)	0.839
Walking for exercise, n (%)	71 (43.6)	15 (38.5)	0.563
Diabetes (n, %)	9 (5.52)	1 (2.56)	0.691
Osteoporosis (n, %)	15 (9.38)	5 (12.82)	0.521
History of Fracture since 50 (n, %)	70 (42.9)	19 (48.7)	0.514
Maternal history of fracture	32 (24.81)	14 (41.18)	0.059
NSAID use (n, %)	38 (23.31)	9 (23.08)	0.975
Current HRT use (n, %)	13 (7.98)	0 (0.0)	0.077
Glucocorticoid use (n, %)	13 (7.98)	3 (7.69)	1.000
Dental examination (n, %)			
Less than 6 months	119 (73.0)	31 (79.5)	0.564
One year ago	30 (18.4)	4 (10.3)	
Two year ago	6 (3.7)	1 (2.6)	
> 2 yrs ago	8 (4.9)	8 (4.9)	

Table 2.4 Age adjusted BMD and annualized percent change in BMD by periodontal status (N=202) (comments, n=51 not availed)

	Periodontal Disease		P-value
	Yes (n=163)	No (n=39)	
BMD (g/cm2)			
Total Hip	0.74 (0.01)	0.74 (0.02)	0.991
Femoral Neck	0.63 (0.01)	0.63 (0.02)	0.839
Intertrochanter	0.87 (0.01)	0.87 (0.02)	0.928
Trochanter	0.56 (0.01)	0.57 (0.02)	0.931
Absolute rate of change in BMD (g/cm2,yr)			
Total Hip	-4.17 (0.70)	-3.94 (1.44)	0.888
Femoral Neck	-2.76 (0.70)	-3.08 (1.43)	0.844
Intertrochanter	-4.48 (0.91)	-4.50 (1.87)	0.994
Trochanter	-2.76 (0.68)	-3.45 (1.40)	0.657
Percentage rate of change in BMD (%/yr)			
Total Hip	-0.54 (0.10)	-0.59 (0.20)	0.906
Femoral Neck	-0.42 (0.11)	-0.50 (0.23)	0.756
Intertrochanter	-0.53 (0.11)	-0.65 (0.25)	0.837
Trochanter	-0.47 (0.12)	-0.58 (0.22)	0.504

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3.0 CHAPTER THREE

THE EFFECT OF ANDROGEN DEPRIVATION THERAPY ON PERIODONTAL DISEASE IN MEN, WITH A CONSIDERATION OF THE RELATIONSHIPS BETWEEN PERIODONTAL DISEASE AND BONE LOSS ON MEN WITH PROSTATE CANCER

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3.1 Abstract of the research

Purpose: To test the hypothesis that men undergoing androgen deprivation (ADT) as treatment for prostate cancer are at greater risk of periodontitis and tooth loss.

Materials and Methods: Eighty-one (81) men with prostate cancer (mean age 68.5 years) were recruited among 325 enrolled in an osteoporosis study. Of these, 68 men were eligible to participate in this study. The prevalence of periodontal disease among men with prostate cancer (n=41) undergoing androgen deprivation (mean years treated=1.5) was compared to men with prostate cancer not undergoing androgen deprivation (n=27, the controls). The prevalence of periodontal disease was examined in relationship to bone mineral density (BMD) among men with prostate cancer both with and without ADT.

Outcome Measures: A periodontist blinded to ADT status recorded probing depth; periodontal attachment loss; bleeding; Plaque Index; gingival recession; missing teeth; and calculus. Logistic regression models tested the association between ADT and periodontal disease. Linear regression models assessed the association between periodontal disease and bone mineral density among both groups with prostate cancer (treated/untreated). We adjusted for variables known to influence periodontal disease including age, race, smoking, history of periodontal disease.

Results: The prevalence of periodontal disease was 80.5% (n=33) among men on ADT compared with 3.7% (n=1) among men not on ADT, odds ratio (95%confidence interval) =3.33(1.07-10.04). Men on ADT had significantly greater probing depth (p<0.001) and a higher plaque index (p<0.09). Eighty-one men (76.9 %) undergoing ADT and the controls completed bone density exams. There was no relationship between bone mineral density and periodontal disease.

Conclusions: Men with prostate cancer undergoing ADT were more likely to have periodontal disease than men not on ADT. If confirmed in larger studies, this observation could have important public health implications given the increasing use of androgen deprivation therapy to treat prostate cancer.

3.2 Background and rationale for the research

Carcinoma of the prostate is the most frequently diagnosed malignancy and the second leading cause of cancer death among men in the western world. The peripheral blockage of androgen action remains a critical therapeutic option in the treatment of prostate cancer. However, androgen deprivation therapy (ADT), the most effective systemic therapy for prostate cancer, is a major risk factor for male osteoporosis (Ross and Small 2002; Wei 1999; Diamond 1998; Morote 2003; Deng 2004). Androgen deprivation therapy causes increased osteoclastic activity (Higano 1983), bone resorption (Seeman 1997), and bone loss (Seeman 2004). Rates of bone loss ranged from 2 percent to 8 percent in the lumbar spine and from 1.8 percent to 6.5 percent in the femoral neck during the initial twelve months of continuous androgen deprivation therapy (Wei 1999; Higano 2003). An increased risk of fracture in men with prostate carcinoma who were treated with androgen deprivation therapy was also observed (Seeman 1983).

Periodontal disease results in resorption of alveolar bone and loss of the soft tissue attachment to the tooth. There is biological plausibility that periodontal destruction may be adversely influenced by systemic bone loss (Rees 2003; Albandar 1990 and 2002; Slots 2003; Nunn 2003; Genco 1996). None of this previous research, however, has examined the link between androgen deprivation therapy with periodontal disease. The incidence of periodontal disease increases with advancing age, and current demographic shifts in the age distribution will lead to increases in the number of people with periodontal disease.

The purpose of the present study was to compare the prevalence of periodontal disease in men with prostate cancer receiving androgen deprivation therapy, with a control group of men with prostate cancer who were not receiving androgen deprivation therapy. In addition we examined the relationship between periodontal disease and measures of bone mineral density in these men.

3.3 The design/setting/patients and the materials and methods of the research

A total of 81 men (mean age 68.5 years) agreed to participate in this periodontal disease study. All men were recruited from a larger group of 325 ambulatory men participating in a study of bone loss in men with non-metastatic prostate cancer being treated with androgen deprivation therapy (ADT) or men not receiving androgen deprivation therapy.

To be eligible for enrollment in the current ancillary research, the men had to be willing to submit to a comprehensive periodontal dental examination, and be willing to sign a University of Pittsburgh

Institutional Review Board (IRB)-approved consent form to participate in the current research. Exclusion criteria for this study were (1) the presence of medical conditions that preclude conducting an adequate oral examination, such as a history of heart disease or joint replacement or any medical disease that requires pre-medication with an antibiotic before a periodontal exam; (2) mental or legal incapacitation so that informed consent cannot be obtained; and (3) history or evidence of metabolic bone disease including hypercalcemia, hyperparathyroidism, Paget's disease of bone, osteomalacia, or osteogenesis imperfecta; and (4) hyperthyroidism or hypothyroidism recognized within six months of study enrollment. The total number of men excluded was 13 (11 edentulisum and two due to medical problem), leaving 68 men participating.

Periodontal assessment

A periodontist (PF), blinded to treatment status, completed comprehensive periodontal examinations [probing depth, clinical attachment loss, bleeding upon probing, Plaque Index, gingival recession, missing teeth, and calculus] on each subject. Probing depth was measured from the gingival margin with the use of a calibrated probe (*HuFriedy Michigan 0 probe*, diameter of probe is 0.5 mm, *HuFriedy Chicago IL*). Probing depth was measured on six sites per tooth (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual). The loss of clinical attachment is defined as the distance, in millimeters (mm), from the cementoenamel junction (CEJ) to the base of the periodontal pocket. A subject was considered to have clinical presence of periodontal disease if he had more than 3mm or more of attachment loss (Weyant *et al.* 1999), as the definitive diagnostic marker. Probing depth is the distance from the free gingival margin (FGM) to the base of the sulcus/pocket. Gingival bleeding was coded as (0: no bleeding; 1: bleeding); supragingival plaque was coded (0: no plaque; 1: plaque), and calculus was measured as (0: no calculus; 1: supragingival calculus). All missing teeth were recorded on a standard dental form. History of periodontal disease, dental hygiene, frequency of tooth brushing, frequency of flossing, and visits to the dentist were also recorded (Weyant et al. 1999).

BMD measurement

Bone mineral density of the spine and hip was measured by using Fan-beam dual energy X-ray absorptiometry (DXA), using a QDR4500 A (Hologic, Inc., Bedford MA). Standardized procedures for patient positioning and scan analysis executed. A spine phantom was scanned daily and indicated no shifts or drifts in scanner performance.

Statistical analysis

Prior to statistical analysis, all data were screened for accuracy. *Log Exact*™ software was used to analyze the data. Descriptive statistics were calculated for all variables including mean, standard deviations, ranges, and percentages. Logistic regression models were used to compare the prevalence of periodontal disease *vs*. the absence of periodontal disease, and presented as odds ratios [OR] including

95% confidence intervals. Linear regressions were used to examine BMD and its relation to periodontal disease.

All models were initially adjusted for age. Multivariable adjusted models included variables known to influence periodontal disease, specifically age, smoking, flossing, brushing, and visits made to the dentist and history of periodontal disease (Albandar 1990 and 2000; Slots 2003; Nunn 2003; Genco 1996; Eggert 2001; Grossi; van Winkellhoff 2001)

3.4 The results of the research, as described for this chapter

Sixty-eight men were examined, including 27 men with prostate cancer not undergoing androgen deprivation therapy and 41 men with prostate cancer receiving androgen deprivation therapy for varying lengths of time. Eleven men (13.6 per cent) were edentulous and were counted among those thirteen individuals excluded from further analysis. The prevalence of edentulism did not differ between men undergoing androgen deprivation therapy and those men not undergoing androgen deprivation therapy. Completing the comprehensive periodontal exam was not possible on two subjects, due to their compromised medical condition, leaving 68 men for the final analysis.

The mean age of the men undergoing androgen deprivation was 70.5 years, and 68.5 years among men not undergoing androgen deprivation therapy (p=0.09). A higher proportion of men undergoing androgen deprivation therapy were 65 years of age or older *(Table 3.1).* There were no statistical differences in age, race, education, or smoking between the two groups. Three men among those undergoing androgen deprivation therapy (7.32 percent) had a history of periodontal disease extending two or more years in treatment, compared with eight percent of men not on androgen deprivation therapy. Although there were no differences in dental hygiene habits [brushing, flossing, visits to the dentist] between the men undergoing androgen deprivation therapy and those who were not, overall the men had excellent hygiene habits, with fifty percent brushing twice a day, and about sixty percent daily flossing. The bulk of the set (46 percent) visited the dentist regularly, at the recommended yearly intervals. Few men had any missing teeth or dental caries (p=1). Nevertheless, eighty-two percent (34 men) of the men undergoing androgen deprivation therapy had moderate plaque (p=0.09), and sixty-eight percent (28 men) had bleeding upon probing (p=0.001).

Periodontal disease

The majority of subjects receiving androgen deprivation therapy had evidence of periodontal disease. These and other indices of periodontal disease are summarized in *Table 3.2*. Among the 68 subjects, thirty-three (33) men (80.95 percent) had periodontal disease compared to one man (3.75 percent) not receiving androgen deprivation therapy who had periodontal disease. Men receiving androgen deprivation therapy

had greater pocket depth (>3mm) and were more prone to attachment loss, recession, and tooth mobility. Tooth mobility was present in 14.4 percent of men undergoing androgen deprivation therapy, and not present in men who were not on androgen deprivation therapy *(p=0.074).*

In unadjusted models, the odds of developing periodontal disease were three-fold greater among men on androgen deprivation therapy compared with men not receiving androgen deprivation therapy *(Table 3.3).* Adjustments for age attenuated this association but it remained borderline significant. Further adjustments for smoking, race, and history of periodontal disease had little effect.

We examined the relationship between periodontal disease and bone mineral density in these subjects. As shown in *Table 3.4*, bone mineral density was similar in both men with and without periodontal disease after adjusting for ADT.

3.5 A discussion of the research, as described for this chapter

We found that the prevalence of periodontal disease was about three times greater in the group undergoing androgen deprivation therapy compared with the group not receiving androgen deprivation therapy, even after we adjusted for age, race, smoking and history of periodontal treatment. To our knowledge this is the first report of a higher prevalence of periodontal disease in men on ADT. If confirmed in other larger studies, this observation could have major public health consequences given the increasing number of men with prostate cancer and the increasing use of ADT to treat these men. Many patients are now being diagnosed with early or progressive disease on the basis of a rising prostate-specific antigen level alone, and hormonal therapy is being employed earlier in the course of the disease. As a consequence, many patients are being treated with hormonal therapy at the asymptomatic stage and, by virtue of the natural history of the disease, survive for years after diagnosis (Rashid and Chaudhary 2004). Clinicians treating men with ADT need to be aware of the increased need for dental visits to identify periodontal disease at the earliest stages, before tooth loss occurs.

Although the majority of individuals in this group were highly educated, visited the dentist regularly, and had very good plaque control, they had periodontal disease. Investigators have previously demonstrated that androgen deprivation therapy causes severe bone loss and osteoporosis, and this may represent the underlying factor which contributes to a relationship between periodontal disease and ADT. Androgen deprivation therapy may enhance rapid bone loss around the teeth, and initiate or accelerate periodontal disease, despite good plaque control. This condition appears to parallel an aggressive type of periodontal disease in which bone loss will happen in a short period of time despite the presence of minimal plaque, and good plaque control. In the presence of androgen ablation therapy other as-yet-

unknown elements may influence the impact of local factors like plaque that can cause or aggravate periodontal disease.

The collective data reported in most of the published cross-sectional studies investigating the relationship between periodontal disease and bone loss or bone turnover appears to indicate a relationship between systemic bone mineral density and oral bone mineral density, but the sample size on all these studies was very small and only one investigator (Jeffcoat 1998) adjusted for age. Generally, most researchers used differing populations and did not adjust for essential covariants such as smoking. The exception to this is Kribbs, studying both normal and osteoporotic women (1990), who showed twenty percent less mandibular density as measured by quantitative analysis of intra-oral radiographs. Our previous study found a correlation between tooth loss and diminished systemic bone mineral density (Famili.et.al 2005). The research is strongest among reports of oral bone loss in osteoporotic women.

Interpretations of the present study may be limited since periodontal measures of bone density or loss, such as subtraction radiography or Shei bone score measurements, were not available to the investigators. Additionally the sample size was small. A larger sample coupled with longitudinal analysis is needed to confirm these findings. However, the current research is significant in that the impact of androgen deprivation therapy on periodontal disease has not been reported before.

We conclude there is an association between periodontal disease and androgen deprivation therapy. This may be due to the osteoporotic bone loss among the group of men receiving androgen deprivation therapy although there was no significant correlation between periodontal disease and bone mineral density in our study. Additional studies utilizing a larger sample size and longitudinal analyses are necessary to definitively correlate periodontal disease and androgen deprivation therapy. If these associations can be confirmed by research conducted with larger sample sizes, this observation may have important public health implications.

Funding for this research was made available, in part, through the Osteoporosis Prevention and Treatment Center at the University of Pittsburgh, which receives support through the National Institutes of Health (K24 DK 062895-01) and the General Clinical Research Center of the University of Pittsburgh Medical Center (M01-RR0056).

Table 3.1
Characteristics of men with prostate cancer with and without undergoing anti-androgen therapy (n=68)

	No ADT (n=27)	**ADT (n=41)**	***p* value for exact test**
Age (mean+/-st)			
<=65	5(22.22)	8(19.51)	.098
65-75	20(70.37)	21(51.22)	
75+	2(7.41)	12(29.27)	
Race			
White	24(88.89)	38(92.68)	.675
Black	3(11.11)	3(7.320	
Education level			
High School	9(33.33)	14(34.15)	.781
College	8(29.63)	15(36.59)	
Beyond college	10(37.04)	12(29.27)	
Current smoker			
Yes	1(3.70)	3(7.32)	0.64
Former smoker (N, %)	2(.20)	8(.80)	0.51
Alcohol drinking (N, %)	27(39.71)	41(60.29)	0.41
Heart disease			
No	26(96.30)	40(97.56)	1.000
Yes	1(3.70)	1(2.44)	
Kidney disease	27(39.71)	41(60.29)	
Brush teeth			
Once a day	5(18.52)	13(31.71)	.540
Twice a day	16(59.26)	20(48.78)	
More than twice a day	6(22.22)	8(19.51)	
Floss			
No	14(51.85)	24(58.54)	
Yes	13(48.15)	17(41.46)	.625
Visit DMD/DDS			
Every six months	12(44.44)	12(29.27)	
Every year	9(33.33)	19(46.34)	
For emergencies	2(22.22)	10(24.39)	.461
Missing teeth			
No	2(7.41)	1(2.44)	.558
Yes	25(92.59)	40(97.56)	
Caries			
No	26(96.30)	38(92.68)	1.000
Yes	1(3.70)	3(7.32)	
Wears dentures			
No	27(100.00)	40(97.56)	1.000
Yes	0(0)	1(2.44)	
Plaque			
Mild	20(74.07)	7(17.07)	<.09
Moderate	7(25.93)	34(82.93)	
Bleeding			
No	20(74.07)	13(31.71)	.001
Yes	7(25.93)	28(68.29)	
History of periodontal disease			
One year	27(100.00)	38(92.68)	.271
Two ore more years	0(0)	3(7.32)	

Table 3.2.
Periodontal disease characteristics of men with prostate cancer with and without androgen deprivation therapy

	Not receiving androgen deprivation therapy	Receiving androgen deprivation therapy	*P* value for exact test
Periodontal disease No	26(96.30)	8(19.51)	.006
Yes	27(3.70)	41(80.49)	
Pocket			
2-3	26(96.30)	0(0)	<.001
3-4	1(3.70)	41(100.00)	
Attachment loss			
No	25(92.59)	0(0)	<.001
Yes	2(7.41)	41(100.00)	
Recession present			
No	20(92.59)	4(9.76)	<.001
Yes	7(7.41)	37(90.24)	
Mobility present			
No	27(100.00)	35(85.37)	.074
Yes	0.00	6(14.63)	

Table 3.3
Odds Ratio [OR] (95 percent confidence intervals) of periodontal disease by androgen deprivation therapy

Model order	Adjustment by	OR	SE	P	95% CI		*p value*
					Lower	Upper	
1	No adjustment	3.333	1.927	0.037	1.073	10.352	0.037
2	Age	2.977	1.817	0.074	0.900	9.849	0.074
3	Age, race	3.149	1.956	0.065	0.932	10.640	0.065
4	Age, smoker	3.122	1.921	0.064	0.935	10.427	0.064
5	Age, race, smoking, history of periodontal treatment	3.201	1.991	0.061	0.946	10.835	0.061

Table 3.4
Bone mineral density in men with and without periodontal disease, adjusted for receiving androgen deprivation therapy

	With periodontal disease	Without periodontal disease	*p value for exact test*
(n undergoing androgen deprivation therapy)	33(80.49)	8(19.51)	.006
Femoral neck BMD(g/cm^2)	.76(.15)	.77(.12)	.797
Total hip BMD(g/cm^2)	.97(.16)	.96(.14)	.986
Lumbar spine(g/cm^2)	1.00(0.17)	1.05(0.16)	.256

3.6 The literature cited in the chapter summary of the research

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4.0 SUMMARY AND CONCLUSIONS

THE RELATIONSHIPS BETWEEN PERIODONTAL DISEASE AND BONE LOSS ON MEN WITH PROSTATE CANCER UNDER ANDROGEN DEPRIVATION THERAPY. A BRIEF SUMMARY ANALYSIS OF THE RESEARCH CONDUCTED, AND A DISCUSSION OF THE RELATED ISSUES, LIMITATIONS, AND CONCLUSIONS OF THE RESEARCH AND THE DISSERTATION

Periodontitis is a multi-factorial disease with microbial dental plaque as the initiator (Genco 1996; Nunn 2003). The manifestation and progression of periodontitis is influenced by a wide variety of determinants and risk factors, including subject characteristics, social and behavioral factors, systemic factors, genetic factors, the microbial composition of dental plaque, and others (Genco 1996; Nunn 2003; Slots 2003). If periodontitis is not treated, the disease will slowly progress and painlessly destroy the bone which supports the teeth. Untreated, the disease will eventually cause tooth loss.

Osteoporosis, or porous bone, is characterized by reduced bone mass and structural deterioration of bone tissue, leading to abnormal bone architecture, fragility of bone, and increased risk of fragility fracture, particularly of the hip, spine, and wrist. Osteoporosis is a major American public health threat---as the first-ever Surgeon General's Report on bone health and osteoporosis made clear with its release on October 14, 2004---and approximately 1.5 million Americans will suffer fragility fractures each year, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites. Ten million Americans already have osteoporosis, and 34 million more have low bone mass, placing them at risk for osteoporosis (Surgeon General's Report 2004). Half of all women and one-quarter of men over 50 will have an osteoporosis-related bone fracture in their lifetimes.

The costs, the Surgeon General points out, are tremendous: A fracture can be the beginning of the deterioration of physical and mental health. Even among individuals who can remain independent, a fracture diminishes the quality of life. The Surgeon General estimates that approximately 20 percent of elderly individuals who suffer a hip fracture (the colloquial indicating fracture for osteoporosis) will die within a year of the fracture (2004).

In fact, as osteoporosis researchers Steven R. Cummings and Joseph Melton summed up in *The Lancet* in 2002, osteoporosis has clinical and public health importance only because of these fractures, causing disability and contributing to health care costs.

Osteoporosis in men has profound clinical implications (Seeman 2001 and 2004; Slots 2003). Osteoporosis is a significant health problem and contributor to disability and premature mortality among older men. Osteoporosis occurring in middle-aged and elderly men is commonly associated with alcohol abuse, smoking, immobilization, and medications. Estimated national direct expenditures (hospitals and

nursing homes) for osteoporosis and related fractures are $18 billion each year (U.S. Surgeon General 2004); men comprise one-third of all osteoporosis cases, and account for one-third of the national health care expense deriving from osteoporosis care.

The issue of the morbidity of osteoporotic hip fractures is addressed directly by research published just this year by the well-respected Swedish investigator John A. Kanis, who has made a career of evaluating the economics of osteoporosis (Johnell and Kanis 2005). Furthermore, Kanis and the equally well-respected Joseph Melton editorialize in the *Journal of Bone and Mineral Research* (June 2005) about the meaning of the reported incidence of hip fracture trends on osteoporosis treatment, concluding that clinicians and the population may be paying better attention to controlling the causes of hip fracture risk (falls and fragility) and that specific programs of selective screening and aggressive treatment to prevent bone loss may really be able to reduce population fracture rates over the short term (Melton Kanis Johnell 2005).

The Surgeon General in 2004 called on health professionals to look for "red flags" clinically and in research that may indicate that an individual or a population is at risk for osteoporosis-related fracture. The relationship between periodontal disease and bone loss is obvious clinically to dentists; examining this relationship further led to the investigation of the relationship between periodontal disease and bone loss and men with prostate cancer who are undergoing androgen deprivation therapy.

The overall prevalence of edentulism in the population of older women that we researched (*Chapter Two*) was higher (36 percent), compared with the 23 percent edentulism rate reported for the U.S. population for women 70 to 74 years as published in the NHANES III study. The higher prevalence observed in our study could have reflected a continued increase in edentulism with advancing age. The women in our study ranged from 73 to 84 years in age. We found little evidence to support an association between osteoporosis and edentulism. Bone mineral density (BMD) and rate of bone loss were similar in these two groups even after adjustments for established correlating factors of edentulism.

Tooth loss has been observed to be related to bone density in the oral cavity in a limited number of studies. When interpreting results in various regions, it is necessary to remember that tooth loss is highly influenced not only by periodontal disease, but also by local practices of the dental community as well as other factors related to oral health. The majority (80 percent) of dentate women had some evidence of periodontal disease (p=0.07). We found no statistically significant associations between periodontal disease variables (average periodontal attachment loss, average number of sites with bleeding, and average number of sites with calculus) and bone mineral density at trochanter, inter-trochanter and femoral neck either cross-sectionally or longitudinally. This was true even after controlling for age, weight, and other important correlating factors. A possible explanation of our lack of an association between periodontal disease and bone mineral density may be because our population was older, and were

missing a large number of teeth. We have no information on the reasons for missing teeth. This finding could be due to periodontal disease that occurred much earlier in a given subject's life. Historical events such as tooth loss can alter the interpretation of the current status of any given subject's periodontal disease. Loss of several periodontally-involved teeth can also result in an improvement of periodontal summary scores such as average loss of attachment.

Compared to the other NHANES III studies, where average attachment loss for the U.S. population was reported to be 2.1mm, our data showed an average attachment loss of 2.49mm. The major strengths of this study (*again, Chapter Two)* are its large sample size and well-controlled measurement of variables, which could confound relationships with bone mineral density. The sample is drawn randomly from a large population of community-dwelling women.

In our current research, studying the effects and relationships of periodontal disease and androgen deprivation therapy in men (*Chapter Three*), the overall prevalence of periodontal disease was very high in the group under androgen deprivation therapy even after we adjusted for age, race, smoking and history of periodontal treatment. Our review of the literature indicated that other comparisons between periodontal disease and androgen deprivation therapy have not yet been reported, so we cannot compare our findings to any others.

The majority of men under androgen deprivation therapy nevertheless had some evidence of periodontal disease ($p<0.01$). We found statistically significant associations between periodontal disease variables (these being *average periodontal attachment loss, pocket depth, recession, average number of sites with bleeding,* and *plaque*) and androgen deprivation therapy, that we have summarized as *Table 3.2* in that chapter. These associations held true even after controlling for past history of periodontal treatment, age, race, and smoking

Although the majority of individuals in this group were highly educated, visited the dentist regularly, and had very good plaque control, they had periodontal disease because they were undergoing androgen deprivation therapy. As the original study of bone loss in men with prostate cancer (by Greenspan in 2004) demonstrated, undergoing androgen deprivation therapy causes severe bone loss and osteoporosis, and may also precipitate rapid bone loss around the teeth and the presence of periodontal disease, even with good plaque control. This situation creates a scenario similar to an aggressive type of periodontal disease in which bone loss will happen in a short period of time despite the presence of minimal plaque. In the presence of androgen ablation therapy, there may be other factors at work besides the influence of local factors like plaque that can cause or aggravate periodontal disease.

4.1 The limitations of the research

The obvious empirical strength of our first study (*Chapter Two*) was its large sample size, drawn randomly from a large population of community-dwelling women, and its well–controlled measurement of variables.

We believe that the current research avenue (studying the effects and relationships of periodontal disease and androgen deprivation therapy in men (*Chapter Three*), is significant in that these observations have never been reported before. Only a limited amount of research relates osteoporosis in men to the presence of androgen deprivation therapy, and the authors believe that ours is the first empirical data relating the presence of androgen deprivation therapy to rapid bone loss around the teeth.

Interpretations of the first study were limited because measurement of bone loss around the teeth was not available, and we had only a single record of periodontal assessment. Interpretations of the present study may be also limited, since periodontal measures of bone density or loss, such as subtraction radiography or Shei bone score measurement, were not available to the investigators, and the sample size addressed here is admittedly small. A larger research sample and longitudinal analysis is necessary to confirm this finding.

4.2 Conclusions, and future recommendations for research

We found small evidence of an association between periodontal disease and longitudinal changes in bone mineral density in this older women population reported in *Chapter Two;* in the subsequent research reported here in men (*Chapter Three*), we conclude that evidence of a strong association between androgen deprivation therapy and periodontal disease exists in the corresponding male population. Additional studies utilizing a larger sample size and longitudinal analysis may be necessary to correlate periodontal disease and changes in bone mineral density due to androgen deprivation.

Considering the relationship among bone mineral density, osteoporosis, and periodontitis in men, it is known that men completing androgen ablation therapy for control of prostate cancer are at higher risk for osteoporosis. As androgen deprivation therapy is the recommended treatment for men with metastatic or locally-advanced non-metatstatic prostate carcinoma, and as prostate carcinoma is the most common visceral malignancy and the second leading cause of death from cancer in men, the relationship between androgen deprivation therapy and loss of bone mineral density is a matter of public health importance.

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